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THE MOLECULAR ELECTROSTATIC POTENTIAL: A TOOL FOR UNDERSTANDING AND PREDICTING MOLECULAR INTERACTIONS

by

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The use of the electrostatic potential in analyzing and predicting molecular interactive behavior and properties has increased remarkably over the past 25 years. In 1980, it was still reasonable to hope to at least mention, in one lengthy review chapter, all of the papers that had been published in this area. In 1996, such an objective would be ridiculous. This popularity can be attributed to (a) the insight that $V(\mathbf{r})$ can provide, especially into noncovalent interactions, and (b) the widespread availability of computational software packages of which it has become a standard feature.

In this chapter, we sought to convey some appreciation of the sort of questions that can and have been addressed by means of the electrostatic potential, and further to indicate some possible future directions. In particular, we believe that quantities derived from $V(\mathbf{r})$, such as Π and σ^2_{tot}, will find increasing application in quantitatively describing macroscopic properties based on noncovalent interactions. Biological systems should provide some fruitful areas for exploration, e.g. drug-receptor binding constants. Overall, a continuing extensive use of the electrostatic potential to analyze an expanding array of phenomena can be anticipated.

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The Molecular Electrostatic Potential: A Tool for Understanding and Predicting Molecular Interactions

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I. Introduction

The quest for improved methods for elucidating and predicting the reactive behavior of molecules and other chemical species is a continuing theme of theoretical chemistry. This has led to the introduction of a variety of indices of reactivity; some are rather arbitrary, while others are more or less directly related to real physical properties. They have been designed and are used to provide some quantitative measure of the chemical activities of various sites and/or regions of the molecule.

In this chapter our focus is on one of these indices, the electrostatic potential $V(\mathbf{r})$ that is created in the space around a molecule by its nuclei and electrons. $V(\mathbf{r})$ can be computed rigorously, given the electronic density function $\rho(\mathbf{r})$, by eq. (1).

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

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$. $V(\mathbf{r})$ is the potential created by the static charge distribution of the molecule; it can also be regarded as the exact interaction energy of this charge distribution with a proton situated at the point $\mathbf{r}$. Of course such a proton would in reality produce some polarization of the

molecule's electronic density, which is not taken into account if $\rho(\mathbf{r})$ corresponds to the unperturbed ground state, as is normally the case. Despite this inconsistency, the pioneering work of Scrocco, Tomasi and their collaborators (Bonaccorsi, Scrocco and Tomasi 1970; Bonaccorsi, Scrocco and Tomasi 1971) demonstrated the usefulness of the electrostatic potential as a guide to molecular interactive behavior, a role in which it is now well-established (Berthier et al. 1972; Berthod and Pullman 1975; Berthod and Pullman 1978; Bonaccorsi et al. 1972a; Bonaccorsi et al. 1972b; Bonaccorsi et al. 1975; Giessner-Prettre and Pullman 1975; Lavery, Corbin and Pullman 1982; Lavery, Pullman and Pullman 1980; Lavery and Pullman 1981; Perahia and Pullman 1978; Politzer and Daiker 1981; Politzer, Laurence and Jayasuriya 1985; Politzer and Murray 1990; Politzer and Murray 1991; Politzer and Truhlar 1981; Pullman and Berthod 1976; Pullman and Pullman 1980; Pullman and Pullman 1981b; Scrocco and Tomasi 1973; Scrocco and Tomasi 1978). Until a few years ago, its extensive applications have focused upon either (a) the extrema of $V(\mathbf{r})$, its most negative and (more recently) positive values, or (b) the qualitative pattern of the electrostatic potential's positive and negative regions, plotted either on planes through the molecule or on its surface. More recently, a third approach has been pursued, which involves quantifying certain key features of the overall pattern of the electrostatic potential and relating them to macroscopic properties (Murray et al. 1994; Murray and Politzer 1994). (For a current exposition of a variety of applications of molecular electrostatic potentials, see Murray and Sen (Murray and Sen 1996).)

Unlike many of the other quantities used now and earlier as indices of reactivity, the electrostatic potential $V(\mathbf{r})$ is a real physical property, one that can be

determined experimentally by diffraction methods as well as computationally (Politzer and Truhlar 1981). It is through this potential that a molecule is first "seen" or "felt" by other chemical species. Eq. (1) shows that the potential at any point **r** is the sum of a positive term, representing the contribution of the nuclei, and a negative one, reflecting the distribution of electrons. The sign of $V(\mathbf{r})$ is determined by the term that dominates at the point in question. For a neutral atom, the electrostatic potential is positive everywhere (Politzer and Murray 1991; Sen and Politzer 1989); negative regions arise only in the space surrounding a molecule or an anion.

Our discussion in this chapter will focus on the use of the electrostatic potential as a means to understanding and predicting chemical interactions. First, we will examine some of its properties and important features. Next, we will discuss methodology. Finally we will review some recent applications of the electrostatic potential in areas such as hydrogen bonding, molecular recognition and in understanding and predicting a variety of physicochemical properties related to molecular interactions. Our intent has not been to provide a complete survey of the ways in which the potential has been used, many of which are described elsewhere (Politzer and Daiker 1981; Politzer, Laurence and Jayasuriya 1985; Politzer and Murray 1990; Politzer and Murray 1991; Politzer and Truhlar 1981; Scrocco and Tomasi 1973), but rather to focus on some diverse examples.

II. Background

The expression for $V(\mathbf{r})$, given as eq. (1), follows from the definition of electrical potential, which will be reviewed here. Any distribution of electrical charge creates

a potential $V(\mathbf{r})$ in the surrounding space. For an assembly of point charges Q_i located at positions $\mathbf{r}_i$, this electrical potential is simply a sum of Coulombic potentials, as given in eq. (2).

$$V(\mathbf{r}) = \sum_i \frac{Q_i}{|\mathbf{r}_i - \mathbf{r}|} \tag{2}$$

Q_i may be either positive or negative in sign. If the charge distribution is continuous, then integration replaces the summation in eq. (2), giving eq. (3).

$$V(\mathbf{r}) = \int \frac{D(\mathbf{r}')\,d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \tag{3}$$

$D(\mathbf{r})$ is the total charge density; its sign can vary as a function of $\mathbf{r}$.

If we consider a molecule as having a static but continuous distribution of electronic charge around a rigid nuclear framework, then its electrical or "electrostatic" potential will have a term similar to eq. (2), with Q_i being the positive charges of the nuclei, Z_A, and a term similar to eq. (3), with $D(\mathbf{r})$ being replaced by the electronic density function $\rho(\mathbf{r})$. Since $\rho(\mathbf{r})$ is customarily defined as a positive function [unlike $D(\mathbf{r})$], the second term on the right side of eq. (1) comes in with a negative sign. The net result is eq. (1). Our purpose in reviewing this background is to show explicitly that eq. (1) follows from basic electrostatics.

It should be noted that the electrostatic potential $V(\mathbf{r})$ is related rigorously to the total charge density $D(\mathbf{r})$ through Poisson's equation, eq. (4).

$$\nabla^2 V(\mathbf{r}) = -4\pi D(\mathbf{r}) = 4\pi\rho(\mathbf{r}) - 4\pi\sum_A Z_A \delta(\mathbf{r} - \mathbf{R}_A) \tag{4}$$

$V(\mathbf{r})$ accordingly plays a key role in the very fundamental and rapidly developing area of density functional theory (Parr 1983; Parr and Yang 1989). An important aspect of this has been the development of relationships, both exact and approximate, between the energies of atoms and molecules and the electrostatic potentials at their nuclei (Levy, Clement and Tal 1981; Politzer 1980; Politzer 1981; Politzer 1987). More recently we have shown that the position of the minimum potential along a bond provides us with a realistic set of covalent radii (Wiener et al. 1996) and that its magnitude is related to the bond dissociation energy (Wiener et al. 1997). The significance of these findings is discussed elsewhere (Politzer and Murray 1996).

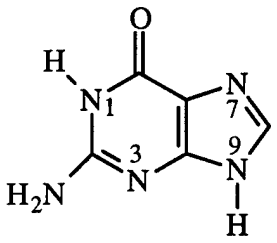
The sign of the electrostatic potential $V(\mathbf{r})$ in any particular region around a molecule, which depends upon whether the effects of the nuclei or electrons are dominant, is a key to assessing its reactivity there. Regions in which $V(\mathbf{r})$ is negative in sign are those to which electrophiles are initially attracted, in particular to the most negative potentials, V_{min}. These V_{min} are typically between 1 and 2 Å from the nuclear framework and associated with one of the following three molecular features: (1) heteroatoms with lone pairs, such as O, N, F, S, P, Cl, Se, As, and Br; (2) pi regions, such as are found in aromatic and double- and triple-bonded systems; and (3) strained bonds (Politzer and Murray 1990).

Sites susceptible to nucleophilic attack can also be identified and ranked by means of positive electrostatic potential regions, but it is necessary to analyze the latter at distances at least 1 to 2 Å away from the nuclei, e.g. in planes removed from the molecular framework (Murray, Lane and Politzer 1990; Politzer, Abrahmsen and Sjoberg 1984; Politzer et al. 1984) or on molecular surfaces

(Murray et al. 1991b; Murray and Politzer 1991; Murray and Politzer 1992; Pullman, Perahia and Cauchy 1979; Sjoberg and Politzer 1990). This is because the electrostatic potentials of atoms and molecules have local maxima only at the nuclei (Pathak and Gadre 1990). To identify sites for nucleophilic attack, it is accordingly necessary to look for the most positive values in planes or on surfaces that are at some distance from the nuclei. (These are of course not true local minima.)

As mentioned earlier, the electrostatic potential around a free neutral atom is positive everywhere (Politzer and Murray 1991; Sen and Politzer 1989), due to the very highly concentrated positive charge of the nucleus in contrast to the dispersed negative charges of the electrons. It is when atoms interact to form molecules that regions of negative potential may and usually do develop as a consequence of the subtle electronic rearrangements that accompany the process.

Figures 1 and 2 show calculated electrostatic potentials for guanine (**1**), in the plane of the molecule and on the molecular surface, respectively. Looking at



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Figures 1 and 2, it can be seen that there are negative potentials associated with N_3, N_7 and the carbonyl oxygen, with the latter two overlapping to form a strong and extensive negative region on one side of the molecule. Both Figures 1 and 2 allow

us to rank N_7 as the site most susceptible to electrophilic interactions, with N_3 and the carbonyl oxygen being fairly similar but less negative than N_7. This is consistent with the experimental observation that N_7 is the favored site for the protonation and alkylation of guanine (Fiskin and Beer 1965; Lawley 1957), with some alkylation also occurring at the oxygen (Friedman, Mahapatra and Stevenson 1963), which is more accessible than N_3 (Figures 1 and 2). Focusing next on positive regions of potential, it is clear that the surface shown in Figure 2 is superior to the contour map in Figure 1 in revealing the relative magnitudes of the positive potentials associated with the hydrogens. Specifically, Figure 2 shows that the hydrogens of the amine group and the one bonded to N_1 are more positive than those on the five-membered ring; the former would accordingly be predicted to be more favored for hydrogen bonding. This is indeed found to be the case; guanine hydrogen bonds to negative sites on cytosine through an amine hydrogen and that on N_1.

Uses of the electrostatic potential that will be emphasized in this chapter will be both qualitative and quantitative. It is important to recognize however that these applications are based on the following exact interpretations of $V(\mathbf{r})$:

1. Given a point charge $\pm Q$ located at the point $\mathbf{r}$, then $\pm QV(\mathbf{r})$ is equal to the electrostatic interaction energy between the unpolarized molecule and the point charge.
2. In a perturbation theory treatment of the total (not just electrostatic) interaction between the molecule and the point charge, $\pm QV(\mathbf{r})$ is the first-order term in the expression for the total interaction energy (which would include polarization and other effects).

3. The negative gradient of $\pm QV(\mathbf{r})$ equals the electrostatic force that is exerted by the molecule's unperturbed charge distribution upon the point charge $\pm Q$.

As just mentioned, $\pm QV(\mathbf{r})$ is an energy quantity. Even though $V(\mathbf{r})$ itself is a potential, not an energy, it is customary to express $V(\mathbf{r})$ in units of energy (e.g., kcal/mole). This is actually $QV(\mathbf{r})$ with Q equal to +1.

Since the electrostatic potential is closely related to the electronic density, it my be useful to discuss how the information that can be obtained from $V(\mathbf{r})$ differs from that provided by the $\rho(\mathbf{r})$. Both are real physical properties, related by eqs. (1) and (4). An important difference between $V(\mathbf{r})$ and $\rho(\mathbf{r})$ is that the electrostatic potential explicitly reflects the net effect of all of the nuclei and electrons at each point in space, whereas the electron density directly represents only the concentration of electrons at each point. A molecule's interactions with another chemical system is affected by its <u>total</u> charge distribution, both positive and negative, and thus can be better understood in terms of its electrostatic potential than its electronic density alone. Examples illustrating this point have been discussed elsewhere (Politzer and Daiker 1981; Politzer and Murray 1991).

III. Methodology

Although eq. (1) is an exact formula for the electrostatic potential due to a set of nuclei $\{Z_A\}$ and an electronic density $\rho(\mathbf{r})$, the latter $[\rho(\mathbf{r})]$ is generally obtained computationally from an *ab initio* or semiempirical wave function or, more recently, from density functional procedures and is therefore necessarily approximate. It follows that the resulting $V(\mathbf{r})$ is also approximate.

Within this framework, given any particular $\rho(\mathbf{r})$, $V(\mathbf{r})$ can be evaluated rigorously (all of the integrals in eq. (1) being calculated exactly) or approximately (Politzer and Daiker 1981). With the ready availability of software packages like the Gaussian series, the former is certainly the more widely used procedure. We will discuss some aspects of this first. We will then briefly examine some approximate methods for obtaining $V(\mathbf{r})$ from $\rho(\mathbf{r})$; detailed analyses of these procedures are found elsewhere (Politzer and Daiker 1981; Politzer, Laurence and Jayasuriya 1985; Tomasi 1982).

A. Dependence of Rigorously-Evaluated V(r) Upon Computational Level

How does a rigorously-calculated electrostatic potential depend upon the computational level at which was obtained $\rho(\mathbf{r})$? Most *ab initio* calculations of $V(\mathbf{r})$ for reasonably sized molecules are based on self-consistent field (SCF) or near Hartree-Fock wavefunctions and therefore do not reflect electron correlation in the computation of $\rho(\mathbf{r})$. It is true that the availability of supercomputers and high-powered work stations has made post-Hartree-Fock calculations of $V(\mathbf{r})$ (which include electron correlation) a realistic possibility even for molecules with 5 to 10 first row atoms; however there is reason to believe that such computational levels are usually not necessary and not warranted. The Møller-Plesset theorem states that properties computed from Hartree-Fock wave functions using one-electron operators, as is $V(\mathbf{r})$, are correct through first order (Møller and Plesset 1934); any errors are no more than second-order effects.

It has been shown that the electrostatic potentials of formamide calculated at near-Hartree-Fock (HF/6-31G*) and post-Hartree-Fock (MP2/6-31G*) levels are qualitatively similar (Politzer and Murray 1991). Both computational approaches predict the oxygen to be the preferred site for electrophilic attack (Seminario, Murray and Politzer 1991). It is further noteworthy that SCF results obtained with minimal basis sets (e.g. HF/STO-3G and HF/STO-5G) are also in good agreement with those calculated at the higher computational levels.

We feel justified in restating our earlier conclusion that varying the *ab initio* computational level does not greatly affect the overall pattern of the electrostatic potential for a given molecule (Politzer and Daiker 1981; Politzer and Murray 1991). There are however certainly differences in detail, the exact locations and magnitudes of the potential minima may change to some degree, and not always predictably (Luque, Illas and Orozco 1990; Politzer and Daiker 1981; Politzer and Murray 1991; Seminario, Murray and Politzer 1991). The key point is that a generally reliable picture of the electrostatic potential can be obtained with an SCF wavefunction, even if only of minimum basis set quality (Boyd and Wang 1989; Daudel et al. 1978; Gatti, MacDougall and Bader 1988; Luque, Illas and Orozco 1990; Politzer and Daiker 1981; Politzer and Murray 1991; Seminario, Murray and Politzer 1991). However we have found that the inclusion of polarization functions for molecules with second-row atoms is recommended, even at the minimal basis set level. There are indications that the semiempirical MNDO and AM1 methods also yield qualitatively reliable electrostatic potentials (Ferenczy, Reynolds and Richards 1990; Luque, Illas and Orozco 1990; Luque and Orozco 1990).

Within the past ten years, density functional procedures (Dahl and Avery 1984; Labanowski and Andzelm 1991; Parr and Yang 1989; Seminario and Politzer 1995) have emerged as an extremely promising alternative to the more traditional *ab initio* and semiempirical procedures for computing molecular properties. Density functional theory is based on the Hohenberg-Kohn theorem (Hohenberg and Kohn 1964), according to which all of the electronic properties of a chemical system, including the energy, are determined by the electronic density. Important features of this approach are that it takes account of electron correlation but nevertheless requires considerably less computer time and space than do comparable *ab initio* techniques. The effectiveness of density functional procedures for computing molecular electrostatic potentials and other molecular properties is still being explored (Labanowski and Andzelm 1991; Laidig 1994; Murray et al. 1992; Seminario and Politzer 1995; Solà et al. 1996). Electrostatic potentials obtained by a local density functional method were shown to be similar to those from SCF calculations (Murray et al. 1992). More recently, analyses of density distributions obtained by density functional techniques (Laidig 1994; Solà et al. 1996) suggest that they provide generally reliable distributions of charge. These results are encouraging in regard to the use of density functional methods for obtaining electrostatic properties.

B. Approximate Evaluation of V(r)

With the continuing surge of development in computing capabilities, approximate methods for evaluating V(**r**) are now generally used only for very large molecular systems, such as those studied in nucleic-acid, protein and other biomolecular research. Historically, the most widely used approximate procedures

for computing the electrostatic potential have been those based upon multipole expansions (Etchebest, Lavery and Pullman 1982; Politzer and Daiker 1981; Rabinowitz, Namboodiri and Weinstein 1986; Tomasi 1982; Williams 1988; Williams 1991). Such representations can approach the rigorously computed $V(\mathbf{r})$ to varying degrees, depending on the number of terms (i.e., quadrupole, octapole, etc.) that are included. Terminating the expansion after the monopole terms [which corresponds to using a set of point charges to obtain $V(\mathbf{r})$] is the simplest possibility, the results of which obviously depend on the number, locations and magnitudes of the point charges (Politzer and Daiker 1981). Overall, this approach has had only limited success. (On the other hand, there continues to be considerable interest in using the molecular electrostatic potential as a basis for obtaining physically-meaningful atomic charges (Besler, Merz and Kollman 1990; Breneman and Wiberg 1990; Chirlian and Francl 1987; Francl et al. 1996; Williams 1991; Williams and Yan 1988; Woods et al. 1990).) Expansions through the quadrupole terms have been shown to yield $V(\mathbf{r})$ comparable with that obtained rigorously from the same $\rho(\mathbf{r})$ (Murray et al. 1990; Rabinowitz, Namboodiri and Weinstein 1986). This success has stemmed from the recognition that an electronic density function written in terms of a gaussian basis set can be expressed as a finite multicenter expansion (Rabinowitz, Namboodiri and Weinstein 1986), with the centers not limited to the nuclei.

Another methodology for computing the electrostatic potential that has been of interest for a number of years involves representing $V(\mathbf{r})$ of large systems as a combination or superposition of contributions from their constituent units or fragments (Bonaccorsi et al. 1980; Nagy, Angyán and Naray-Szabo 1987; Náray-

Szabó 1979; Politzer and Daiker 1981; Pullman and Pullman 1981a; Scrocco and Tomasi 1973; Tomasi 1981). Breneman, quite recently, has developed a method in which V(**r**) is computed from densities obtained through "transferable atom equivalents" (Breneman 1996); the resulting electrostatic potentials are of *ab initio* quality.

IV. Some Applications

A. Analysis of Noncovalent Interactions

Noncovalent interactions, both inter- and intramolecular, are of considerable importance in determining the physical properties of molecules. Such interactions can be classified as hydrogen-bonding or non-hydrogen-bonding. In this section we will explore some recent uses of the electrostatic potential in the analysis of both types.

1. Family-Independent Relationships Between Computed Electrostatic Potentials on Molecular Surfaces and Solute Hydrogen Bond Acidity/Basicity

In view of the well-established importance of the electrostatic component in hydrogen bonding (Benzel and Dykstra 1983; Buckingham and Fowler 1985; Kollman 1977; Legon and Millen 1987; Lin and Dykstra 1986; Umeyama and Morokuma 1977), it is not surprising that the molecular electrostatic potential V(**r**) has been found to be an effective means for analyzing and correlating hydrogen-bonding interactions (Espinosa et al. 1996; Hagelin et al. 1995; Kollman et al. 1975; Leroy, Louterman-Leloup and Ruelle 1976c; Murray and Politzer 1991; Murray and Politzer 1992; Murray, Ranganathan and Politzer 1991; Politzer and

Daiker 1981; Politzer and Murray 1991). For example, it has been used successfully to predict the sites and directionality of hydrogen bonds in a variety of systems, including many hydrogen-bonded dimers (Kollman et al. 1975; Leroy, Louterman-Leloup and Ruelle 1976a; Leroy, Louterman-Leloup and Ruelle 1976b; Leroy, Louterman-Leloup and Ruelle 1976c). Specifically, the positions of the most negative potentials, V_{min}, associated with the hydrogen-bond accepting heteroatoms of isolated gas phase molecules were shown to be effective for predicting the sites and therefore directionality of hydrogen bonds to that particular heteroatom (Kollman et al. 1975; Leroy, Louterman-Leloup and Ruelle 1976a; Leroy, Louterman-Leloup and Ruelle 1976b; Leroy, Louterman-Leloup and Ruelle 1976c). In addition, a good correlation was found between calculated hydrogen bond energies and the value of $V(\mathbf{r})$ at a fixed distance from the hydrogen-bond accepting molecule in a series of complexes between HF and various acceptors (Kollman et al. 1975).

In order to further explore the relationship between the magnitude of the V_{min} in the vicinity of a hydrogen-bond accepting heteroatom and its tendency to form a hydrogen bond, we studied the relationship between V_{min} and the solvent hydrogen-bond-accepting parameter β (Murray, Ranganathan and Politzer 1991). β is one of the "solvatochromic parameters" introduced by Kamlet *et al* (Kamlet et al. 1983; Kamlet, Abboud and Taft 1981; Kamlet et al. 1979; Kamlet, Solomonovici and Taft 1979; Kamlet and Taft 1976) in the course of an extended effort to separate, identify and quantify various types of solvent effects upon experimentally measurable solution properties (e.g. rate constants, equilibrium

constants, and IR, NMR, ESR, and UV/vis absorption maxima and intensities). It is interpreted as providing a measure of a solvent's ability to accept a proton in a solute-to-solvent hydrogen bond (Kamlet et al. 1983). We showed that there exist good correlations between β and V_{min}, computed at the HF/STO-5G*//HF/STO-3G* level, for four series of oxygen- or nitrogen-containing molecules (Murray, Ranganathan and Politzer 1991): azines, primary amines, alkyl ethers, and molecules containing double-bonded oxygens.

The success of this simple approach led us to consider correlating some value of the electrostatic potential associated with a hydrogen-bond-donating molecule with the solvatochromic parameter α. The latter is viewed as indicative of a solvent's ability to donate a proton in a solute-solvent hydrogen bond (Kamlet et al. 1983). Because there are no true maxima associated with any regions of a molecule's $V(\mathbf{r})$ away from its nuclei, we chose to compute the electrostatic potential on molecular surfaces defined by a contour of the electronic density (e.g. the 0.002 au or 0.001 au contour). Good correlations were found between α and the most positive value of the electrostatic potential on the surface, $V_{S,max}$, for a group of –OH and a group of alkyl hydrogen bond donors (Murray and Politzer 1992). These calculations were also carried out at the HF/STO-5G*//HF/STO-3G* level.

In the preceding studies, we had focused upon the hydrogen-bond basicity and acidity of solvents. Our next step was to investigate whether our calculated V_{min} and $V_{S,max}$ would also correlate with Abraham *et al*'s more recently developed scales of solute hydrogen-bond basicity and acidity (Abraham et al.

1988; Abraham et al. 1989a; Abraham et al. 1990; Abraham et al. 1989b), designated β_2^H and α_2^H, respectively. α_2^H and β_2^H had been obtained from equilibrium constants for the formation of 1:1 complexes between a solute molecule and a given reference base or acid, respectively, in CCl_4. We found good correlations between $V_{S,max}$ and α_2^H and V_{min} and β_2^H, for groups of molecules (Murray and Politzer 1992). The relationships are very similar to those found for the solvent parameters α and β (Murray, Ranganathan and Politzer 1991). These findings confirmed that the calculated electrostatic potential, which refers to the molecule in the gas phase, can be quantitatively related to its tendency to form hydrogen bonds in solution, whether as a part of the solvent interacting with a solute or as a solute molecule forming a 1:1 complex with a reference system.

The correlations that have been described are all family-dependent, a different one applying to each different group of structurally-related molecules. Our next objective was accordingly to ascertain whether they could perhaps be made more general by improving the quality of the wave functions used to calculate the electrostatic potentials and, in the case of the hydrogen-bond-acceptor molecules, by using surface electrostatic potential minima ($V_{S,min}$) instead of the three-dimensional spatial minima (V_{min}). Optimized structures and surface electrostatic potentials were computed for eighteen hydrogen-bond-donating and thirty-three hydrogen-bond-accepting molecules, at the HF/6-31G* level (Hagelin et al. 1995).

The eighteen hydrogen-bond-donors are listed in Table 1 along with their experimentally derived and statistically corrected[1] α_2^H values and our calculated $V_{S,max}$. At the HF/6-31G* level, an excellent general correlation was found between α_2^H(corrected) and $V_{s,max}$; the latter is invariably associated with the hydrogen(s) to be donated in the hydrogen bond (Hagelin et al. 1995). This relationship, given as eq. (5), is shown in Figure 3. The correlation coefficient is 0.991 and the standard deviation is 0.04.

$$\alpha_2^H(\text{corrected}) = 0.0196V_{S,max} - 0.556 \qquad (5)$$

For the group of thirty-three hydrogen-bond-accepting molecules in Table 2, we chose to seek correlations directly with the equilibrium constant, K_{HB}, for 1:1 complexation of the acceptors with *p*-fluorophenol. This is because the K_{HB} in Table 2 are from different sources and it seemed preferable to use the actual measured quantity (K_{HB}) rather than one defined in terms of it. As in the case of the hydrogen-bond acidity correlations, we have listed the statistically corrected[2]

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[1]The statistical correction to α_2^H is applied to those molecules having N similar hydrogens available for hydrogen bonding [82]. α_2^H is defined by $\alpha_2^H = (\log K_a + 1.1)/4.636$, where K_a is the equilibrium constant for a 1:1 complex of the donor and a reference acceptor. Then $K_a = \sum_{i=1}^{N} K_{ai} = NK'_a$ where K'_a is the corrected value. Accordingly $\log K_a = \log N + \log K'_a$ and α_2^H (corrected) $= \alpha_2^H - (\log N)/4.636$.

[2]The statistical correction to $\log K_{HB}$ is applied to those molecules having N indistinguishable atoms that can accept a hydrogen bond. Then $K_{HB} = \sum_{i=1}^{N} K_{HBi} = NK'_{HB}$ where K'_{HB} is the corrected value, and $\log K'_{HB} = \log K_{HB} - \log N$.

Table 1. Properties of some hydrogen-bond donors.[a,b]

Molecule	α_2^H	α_2^H (predicted)	$V_{S,max}$ (kcal/mole)
CH_3COCH_3	0.04 (-0.13)	–0.12	22.3
CH_3CN	0.09 (-0.01)	–0.01	27.8
CH_3NO_2	0.12 (0.02)	0.10	33.5
CH_2Cl_2	0.13 (0.07)	0.04	30.2
$CHCl_3$	0.20	0.16	36.7
$C_6H_5NH_2$	0.26 (0.20)	0.15	36.3
CH_3CH_2OH	0.33	0.36	47.0
CH_3OH	0.37	0.38	47.8
pyrrole	0.41	0.39	48.3
indole	0.44	0.41	49.6
CH_3COOH	0.55	0.55	56.4
CF_3CH_2OH	0.57	0.66	62.1
C_6H_5OH	0.60	0.59	58.4
2-naphthol	0.61	0.61	59.7
p-$C_6H_4(Cl)OH$	0.67	0.70	64.1
p-$C_6H_4(OH)NO_2$	0.82	0.86	72.5
$(CF_3)_3COH$	0.86	0.82	70.1
CF_3COOH	0.95	0.88	73.3

[a]The α_2^H values are from R. W. Taft. A statistical correction has been applied to obtain the α_2^H values given in parentheses.

[b]The $V_{S,max}$ and predicted α_2^H values have been reported in reference 91.

values of log K_{HB} in Table 2, along with our calculated $V_{S,min}$ for each molecule (Hagelin et al. 1995). Only four of the acceptor molecules needed statistical corrections; these are $(CH_3CH_2)S_2$, dithiane, dioxane, and pyrimidine, each of which has two identical hydrogen-bond-accepting heteroatoms per molecule.

We found a reasonable general linear relationship between $V_{S,min}$ and the corrected log K_{HB} values, given as eq. (6) and shown in Figure 4.

$$\log K_{HB}(\text{corrected}) = -9.030 \times 10^{-2} V_{S,min} - 2.341 \qquad (6)$$

The correlation coefficient is 0.902 and the standard deviation is 0.39. That this correlation is of a lower quality than that between α_2^H and $V_{S,max}$ may be due in part to the fact that $V_{S,max}$ is always on a hydrogen, while $V_{S,min}$ is on a variety of different heteroatoms.

Overall, we have shown that family-independent correlations can be obtained for solute hydrogen bond acidity and basicity, as quantitated by α_2^H and log K_{HB}. These are well represented at the HF/6-31G* level by an electrostatic potential term alone, $V_{S,max}$ or $V_{S,min}$, respectively (Hagelin et al. 1995).

2. *The Analysis of Non-Hydrogen-Bonding Noncovalent Interactions Using Surface Electrostatic Potentials*

The calculated molecular electrostatic potential is particularly well suited for the analysis of noncovalent interactions, which do not involve making or breaking covalent bonds and which occur without any extensive polarization or charge transfer between the interacting species. As we have discussed in the previous

Table 2. Properties of some hydrogen-bond acceptors.[a,b]

Molecule	log K_{HB}	log K_{HB} (predicted)	$V_{S,min}$ (kcal/mole)
benzene	–0.50	–0.53	–20.1
Cl_3CCN	–0.26	0.29	–29.1
$(CH_3CH_2S)_2$	–0.10 (–0.40)	–0.17	–24.0
$(CH_3CH_2)_2S$	0.11	0.08	–26.9
dithiane	0.24 (–0.06)	–0.26	–23.0
tetramethylsulfide	0.30	0.14	–27.5
ClH_2CCN	0.39	0.87	–35.6
HCO_2CH_3	0.69	1.58	–43.4
$F_3CCH_2NH_2$	0.72	0.39	–30.3
(3,5–Cl_2)pyridine	0.80	0.41	–30.5
C_6H_5CHO	0.80	1.27	–40.0
CH_3OH	0.82	1.27	–40.0
CH_3CN	0.91	1.45	–42.0
$CH_3CO_2CH_3$	1.00	1.32	–40.5
$(CH_3CH_2)_2O$	1.01	0.91	–36.0
CH_3CH_2OH	1.02	1.29	–40.2
dioxane	1.03 (0.73)	0.73	–34.0
CH_3COCH_3	1.18	1.38	–41.2
tetrahydrofuran	1.26	1.33	–40.7
pyrimidine	1.35 (1.05)	0.88	–35.7

(continued)

Table 2. Properties of some hydrogen-bond acceptors (continued).[a,b]

Molecule	log K_{HB}	log K_{HB} (predicted)	$V_{S,min}$ (kcal/mole)
$(CH_3CH_2)_3P{=}S$	1.46	1.00	–37.0
$(CH_3)_2NCN$	1.56	1.88	–46.8
cyclopropylamine	1.64	1.25	–39.8
NH_3	1.68	1.98	–47.8
pyridine	1.88	1.37	–41.1
(4–CH_3)pyridine	2.03	1.51	–42.6
$(CH_3)_2NCHO$	2.10	2.02	–48.3
CH_3NH_2	2.15	1.69	–44.6
$CH_3(CH_2)_3NH_2$	2.17	21.70	–44.7
$(CH_3)_2NCOCH_3$	2.44	2.07	–48.8
$(CH_3)_2S{=}O$	2.53	2.85	–57.5
(1-CH_3)imidazole	2.60	2.20	–50.3
pyridine N-oxide	2.76	2.42	–52.7

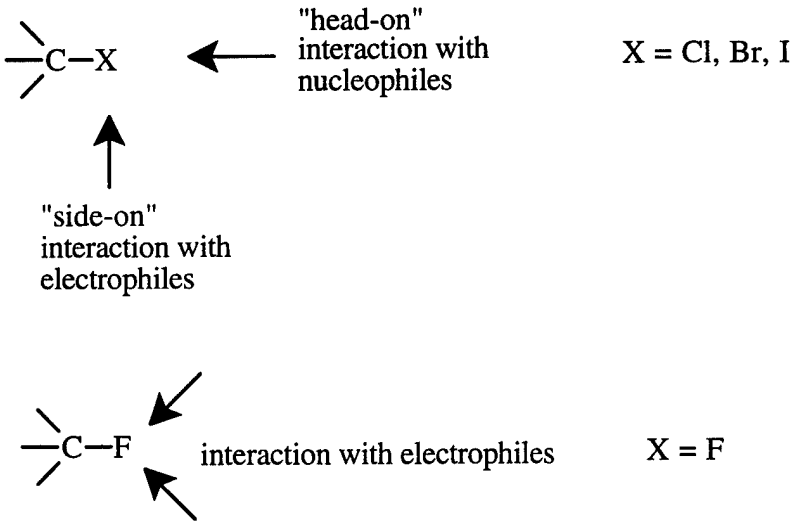
[a]Most of the log K_{HB} values were obtained from M. Berthelot. A statistical correction has been applied to obtain the values in parentheses. All of the data in Table 2 have been reported in reference 91.

section, $V(\mathbf{r})$ has been shown to be useful both as a guide to sites and directional preferences for hydrogen bonds and as an indicator of hydrogen-bond-donating and -accepting tendencies. In this section, we will discuss the application of the

electrostatic potential to the analysis of other types of noncovalent interactions that we will classify as non-hydrogen-bonding.

a. "Halogen" bonding

Certain directional preferences have been observed in the orientations of halogen-containing organic molecules in the crystalline state (Murray-Rust et al. 1983; Ramasubba, Parthasarathy and Murray-Rust 1986). When the halogen X is chlorine, bromine or iodine, electrophilic portions of neighboring molecules generally tend to interact with it in a "side-on" manner, nearly normal to the C–X bond, whereas nucleophilic regions usually interact nearly "head-on", along the C–X axis at the X end (Ramasubba, Parthasarathy and Murray-Rust 1986). However interactions with a fluorine in a C–F bond tend to be only by



electrophiles, with the approaches somewhere intermediate between "side-on" and "head-on". The fact that nucleophiles interact at all with chlorine, bromine and iodine in crystalline organic environments may seem inconsistent with the overall electron-attracting natures of these halogens and the resulting negative electrostatic

potentials associated with them (Murray, Lane and Politzer 1990; Politzer, Laurence and Jayasuriya 1985; Politzer and Murray 1991). However we have recently demonstrated that all of the directional preferences mentioned above can be predicted from an analysis of the potentials computed on the molecular surfaces of a series of halogenated methanes, including CF_4, CCl_4 and CBr_4 (Brinck, Murray and Politzer 1992b).

Our calculated surface electrostatic potentials for CCl_4 and CBr_4 show the anticipated negative regions around the chlorines and bromines, except at the outer ends, which are actually *positive* (Brinck, Murray and Politzer 1992b). The negative rings around the sides of the Cl and Br have surface minima at angles of 102° and 96° with the C–Cl and C–Br axes, respectively. These results are consistent with the observed orientational preferences of both electrophiles and nucleophiles interacting with C–Cl and C–Br bonds in organic crystals. In contrast, the surface potential of CF_4 is negative along the sides *and* at the ends of the fluorines, with the $V_{S,min}$ forming angles of 132° with the C–F bonds (Brinck, Murray and Politzer 1992b). This is consistent with fluorine in organic crystals interacting only with electrophiles and in an intermediate-type orientation.

The positive potentials at the ends of the chlorines and bromines in CCl_4 and CBr_4 suggest that they should be able to interact with negative portions of other systems. This has indeed been observed, e.g. with the π electrons of aromatic rings such as benzene or *p*-xylene (Gotch, Garrett and Zwier 1991; Ham 1953; Hooper 1964) and with the lone pair regions of pyridine (Dumas, Peurichard and Gomel 1978), tetrahydrofuran (Dumas, Peurichard and Gomel 1978), quinuclidine

(**2**) (Blackstock, Lorand and Kochi 1987) and diaza[2.2.2]octane (**3**) (Blackstock, Lorand and Kochi 1987). Lorand and Spek (Lorand and Spek) have introduced the term "halogen-bonding" to designate this type of electrostatic interaction between the ends of the larger halogens (Cl, Br and I) in carbon-halogen bonds and the electron-donating portions of other molecules.

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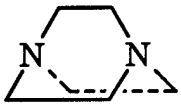

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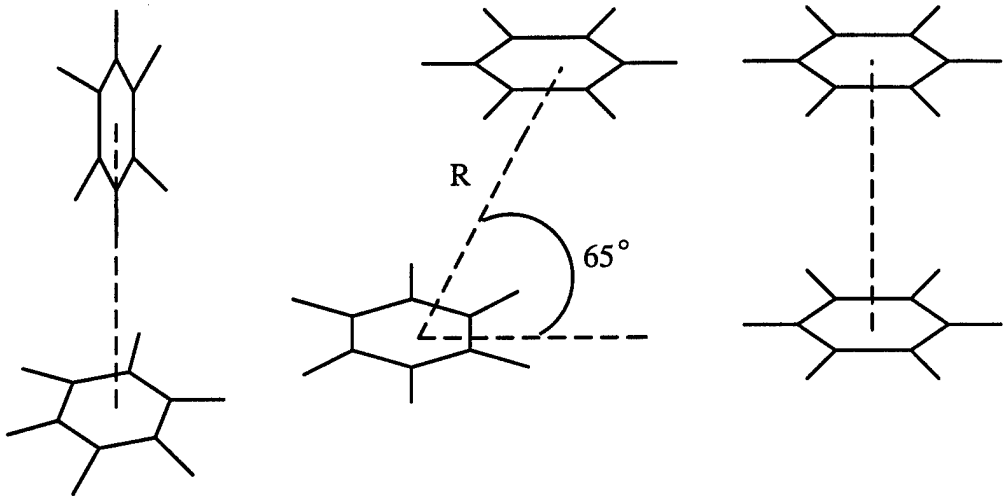
We have also shown that the electrostatic potentials computed on the molecular surfaces of the mixed-halogen derivatives $CHFCl_2$, CF_3Cl, CF_3Br and CF_3I give qualitatively the same pattern as was seen for the methane systems containing only one type of halogen. The fluorines are again negative everywhere, while chlorine, bromine and iodine are negative around the sides but positive at the ends (Murray, Lane and Politzer 1995b; Politzer and Murray 1995).

These results are relevant to spectroscopic studies showing that a variety of hydrogen-free fluorocarbons (e.g. CF_3Cl, C_2F_5Cl, CF_3Br and C_2F_5Br) can act as hydrogen bond breakers (DiPaulo and Sandorfy 1974). This capability has been linked to the anesthetic potencies of halocarbons; it has been suggested that molecules such as CF_3Cl and CF_3Br disrupt preexisiting hydrogen bonds by displacing the proton donors and forming "halogen" bonds.

b. Interactions involving benzene and its derivatives

The surface electrostatic potential of benzene has a symmetrical pattern with negative regions above and below the six-membered ring, due to the π electrons,

and positive regions encircling the molecule with surface maxima associated with the hydrogens (Sjoberg 1989). This simple pattern can explain the existence of both the T-shaped structure (**4**) and the parallel-displaced structure (**5**) that have



4 **5** **6**

been reported experimentally and theoretically for the benzene dimer (Hobza, Selzle and Schlag 1993). On the other hand, this V(**r**) pattern argues against a sandwich-type structure (**6**), and indeed this has been found computationally to be less stable than **4** and **5** (Hobza, Selzle and Schlag 1990). The surface potential of benzene is also consistent with the crystalline orientation of benzene molecules, which is essentially a three-dimensional extension of the T-shaped dimer **4** (Cox et al. 1958).

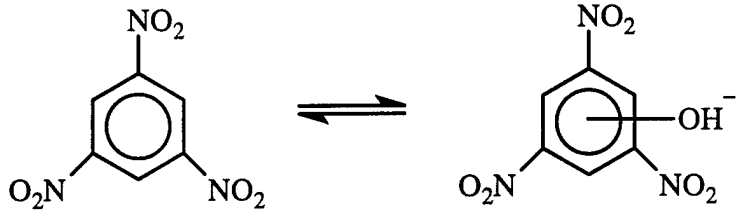
The interactive properties of the derivatives of benzene vary widely, depending upon the nature of the substituent and its influence upon the aromatic ring. The effects of substituents have been categorized and quantified through the introduction of first the Hammett and then the Taft constants, which were obtained

through the analysis of linear free energy relationships (Exner 1988). The electrostatic potentials of benzene derivatives provide another means of ascertaining how the substituents affect the interactive behavior of the aromatic systems (Murray, Paulsen and Politzer 1994).

In the course of a study of the surface electrostatic potentials of a group of C_6H_5X molecules, where X=NH_2, OH, OCH_3, CH_3, F, Cl, Br, I, CHO, CN and NO_2, we have found that the respective surface $V(\mathbf{r})$ can be categorized into three main groups, depending upon whether X is (1) a resonance-donor, (2) strongly electron-withdrawing, or (3) a halogen. Each of these groups will be discussed separately.

The relatively strongly resonance-donating substituents $-NH_2$, –OH and OCH_3 produce very similar surface $V(\mathbf{r})$ patterns (Murray, Paulsen and Politzer 1994). The regions above and below the aromatic rings are more negative than those in benzene, and even stronger negative potentials are found in the vicinities of the heteroatoms (N or O); these are attributed to the lone pair electrons of the heteroatoms. These surface $V(\mathbf{r})$ patterns are consistent with aniline, phenol and anisole acting as bifunctional bases (Berthelot 1992). In toluene, on the other hand, with the weakly electron-donating methyl substituent, the negative regions above and below the ring are only very slightly strengthened relative to benzene. The methyl group does introduce some asymmetry into the surface $V(\mathbf{r})$ pattern, but otherwise changes it relatively little from the that of benzene, suggesting that alkyl substituents should not be classified together with the stronger electron-donors but instead should be viewed as slight perturbations of benzene's hydrogens.

We have found that strongly electron-withdrawing substituents, such as –CN, $–NO_2$ and –CHO, either totally eliminate the negative regions above and below the aromatic ring, as in benzonitrile and nitrobenzene, or significantly weaken them, as in the case of benzaldehyde (Murray, Paulsen and Politzer 1994). Molecules of this type have strong negative regions of potential associated with certain heteroatoms of their functional groups, such as the oxygens of $–NO_2$ and –CHO and the nitrogen of –CN. From an analysis of the electrostatic potentials, it would be predicted that electrophilic intermolecular interactions should occur in the vicinities of these heteroatom negative regions (Murray, Paulsen and Politzer 1994). Indeed Berthelot (Berthelot 1992) has found benzonitrile, nitrobenzene and benzaldehyde to be monofunctional oxygen or nitrogen bases. The positive V(**r**) regions above nitrobenzene and benzonitrile suggest that these may serve as sites for nucleophilic interactions. Indeed our results for nitrobenzene and other nitroaromatics (Murray, Lane and Politzer 1990; Politzer, Abrahmsen and Sjoberg 1984) are consistent with the observed interactions of these molecules with hydroxide and alkoxide ions to form Meisenheimer complexes, e.g. as shown for 1,3,5-trinitrobenzene (**7**) below.



(7)

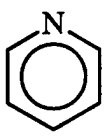
7 π-complex

The monohalogenated derivatives C_6H_5X, where X = F, Cl, Br and I, have negative regions of potentials above and below their aromatic rings (Murray, Paulsen and Politzer 1994). However they are all weaker than those of benzene, due to the net electron-attracting nature of the halogen. There is also a weak negative region associated with each of the halogen atoms. Chloro-, bromo- and iodobenzene have an additional interesting feature; the surface potential at the end of the chlorine, bromine, or iodine is positive (Murray, Paulsen and Politzer 1994), suggesting a tendency for interactions with nucleophiles at these sites ("halogen" bonding), as we have discussed above. The overall pattern of the surface V(**r**) of the halogenated benzenes suggests that they will undergo weak electrophilic interactions above and below their aromatic rings and through the halogens, in addition to weak nucleophilic interactions at the ends of the halogens in chloro-, bromo- and iodobenzene.

The surface electrostatic potentials of benzene derivatives demonstrate how the substituent can significantly alter the pattern of the surface potential. Such effects are a key to understanding and predicting the noncovalent interactions that these types of molecules will undergo.

c. Azine interactions

The surface potentials of the azines pyridine (**8**), pyrimidine (**9**), pyrazine



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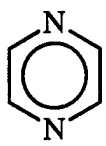

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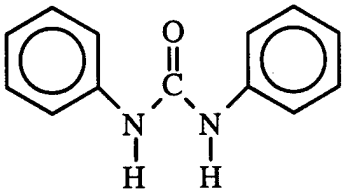
12

(**10**), s-triazine (**11**) and s-tetrazine (**12**) show several distinct patterns. The most negative potentials in each are associated with the ring nitrogens; they become less negative as the number of ring nitrogens increases (Politzer and Murray 1990). Though **8** - **12** are viewed as having varying degrees of aromaticity, only pyridine, **8**, shows any negative region extending above and below the six-membered ring. **9** - **12** have increasingly stronger positive regions of surface potential above the ring. This is in striking contrast to benzene, which is negative in this region.

The surface potentials of **9** - **12** suggest that they will interact with nucleophiles above and below their six-membered rings and with electrophiles through their ring nitrogens. Indeed, the surface potential of **12** helps to explain the formation of its crystal structure, its dimerization, and complexes with other molecules, such as HCl, H_2O and C_2H_2 (Politzer et al. 1992b). For example, in the s-tetrazine crystal, the planes of adjacent molecules are perpendicular to one another (Bertinotti, Giacomello and Liquori 1956), consistent with the negative N–N portions of each being positioned above the positive ring centers of its neighbors.

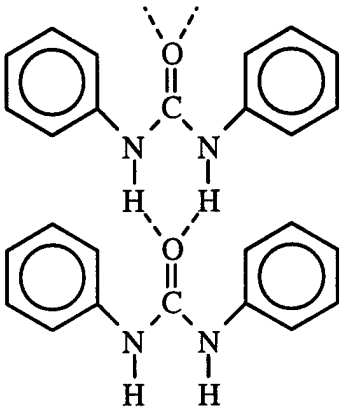
d. Diphenylurea crystallization

1,3-*bis*phenylurea (**13**) is the parent compound of a large family of derivatives, most of which do *not* cocrystallize with guest molecules (Etter et al. 1990). Even when put into solution with strong hydrogen bond acceptors, e.g.



13

dimethyl sulfoxide (DMSO), triphenylphosphineoxide (TPPO) and tetrahydrofuran (THF), most diphenyl ureas crystallize with other molecules of the same kind in a connectivity pattern viewed as is shown below (**14**) instead of forming cocrystals (e.g. **15**).



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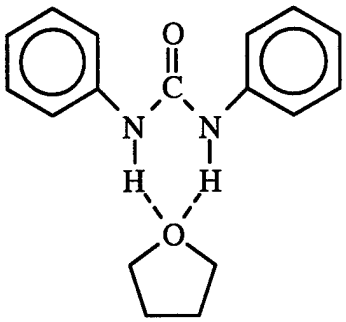

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We have proposed that the tendency for **13** to form homomeric rather than guest-host crystals is largely due to a relatively strong and nonlocalized electrostatic attraction between diphenylurea molecules (Murray et al. 1991a). The surface electrostatic potential of **13**, shown in Figure 3, shows an extended negative region along the top edge of the molecule and a long positive one along the bottom edge. The suggested nonlocalized electrostatic interaction between the top and bottom edges of adjacent molecules, more extensive than hydrogen bonding, apparently provides sufficient stability that homomeric crystal formation is not disrupted even by the presence of very strong hydrogen bond acceptors in solution during crystallization.

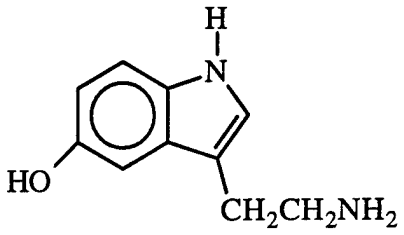
B. Molecular Recognition

The initial step in many important classes of biological processes, including drug-receptor and enzyme-substrate interactions, is one of "recognition." A receptor "recognizes" that an approaching molecule has certain key features that will promote their mutual interaction. This recognition is believed to occur when the two species involved in the interaction are at a relatively large separation and precedes the formation of any covalent bond.

The electrostatic potential $V(\mathbf{r})$ is well suited for analyzing processes based on "recognition", because $V(\mathbf{r})$ is a physically-meaningful representation of how a molecule is perceived by a system in its vicinity. It is through their potentials that the two species involved in the interaction first "see" each other. Therefore, it is not surprising that the electrostatic potential has been shown to be an effective means of analyzing and elucidating recognition processes (Cheney 1982; Hayes and Kollman 1976; Loew and Berkowitz 1975; Martin et al. 1975; Martin et al. 1983a; Martin et al. 1983b; Martinelli and Petrongolo 1980; Murray, Evans and Politzer 1990; Murray et al. 1986; Náray-Szabó 1983; Osman, Weinstein and Topiol 1981; Petrongolo, Preston and Kaufman 1978; Petrongolo and Tomasi 1975; Platt and Silverman 1996; Sheridan and Allen 1981; Spark, Winkler and Andrews 1982; Thomson and Brandt 1983; Weinstein, Osman and Green 1979; Weinstein et al. 1981a; Weinstein et al. 1981b). Several illustrative examples of this use of the electrostatic potential will be summarized below.

The first example involves the molecule 5-hydroxytryptamine (**16**), also known as serotonin and 5-HT. **16** is a neurotransmitter that interacts with receptors both in the brain and in peripheral tissues. The electrostatic potentials of

16 and other hydroxytryptamines have been found to have two characteristic minima on each side (above and below) of the indole portions of the molecules (Weinstein, Osman and Green 1979; Weinstein et al. 1981a; Weinstein et al. 1981b). One of these is associated with the six-membered ring, the other with the



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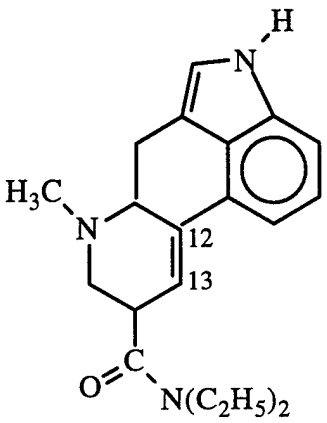
hydroxyl oxygen. An "orientation vector" can be drawn for each hydroxytryptamine, connecting these two minima along the potential gradient between them. It was found that the degree to which the direction of this vector deviates from that in 5-HT is related to the relative affinity of that molecule for 5-HT receptors. Apparently the direction of the vector is indicative of how readily the molecule can achieve the preferred orientation relative to the receptor.

This type of reasoning has explained the experimental finding that 5-HT and *d*-lysergic acid diethylamide, **17** (LSD), act on the same receptors (Weinstein, Osman and Green 1979; Weinstein et al. 1981a; Weinstein et al. 1981b). Thiswould not have been predicted by looking at the structures of **16** and **17**; however, the electrostatic potentials of the two exhibit important similarities. The C_{12}-C_{13} double bond in LSD produces a minimum in $V(\mathbf{r})$ that mimics the one associated with the OH group in **16**. The net result is that the electrostatic potential of **17** shows the key features that are required for the molecule to interact effectively with 5-HT receptors. It is interesting to note that when compound **18**

was tested experimentally, its affinity for an LSD/5-HT receptor was lower by a factor of 10^{-2} than that of either 5-HT or LSD, but comparable to that of tryptamine (5-HT without the hydroxyl group).



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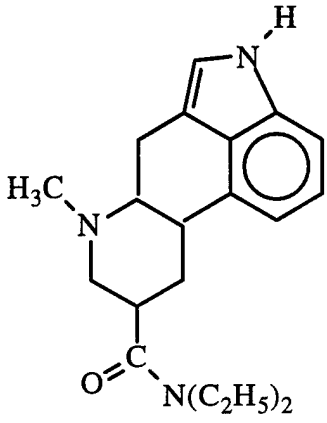

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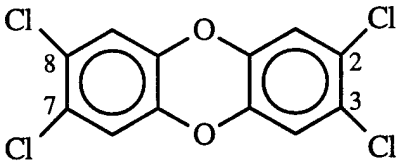
Our second example involves substituted dibenzo-*p*-dioxins and their analogues. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (**19**, TCDD) is the prototype of a group of halogenated aromatic hydrocarbons which have varying degrees of toxicity, ranging from virtually none, for the parent compound dibenzo-*p*-dioxin



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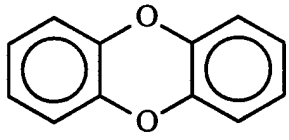

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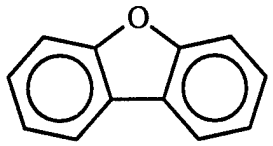
(**20**), to very high, as in the case of TCDD (Long and Hansson 1983; Poland and Knutson 1982). In the course of investigating factors that lead to effective interactions of certain members of this class of compounds with the receptor believed to initiate their toxic responses, we have computed the electrostatic

potentials of **19** and **20**, as well as nine other mono- to tetra- halogenated dibenzo-*p*-dioxins, dibenzofuran (**21**), 2,3,7,8-tetrachlorodibenzofuran (**22**), and three other analogues of TCDD, **23** - **25** (Murray, Evans and Politzer 1990; Murray and Politzer 1987; Murray et al. 1986; Politzer 1988; Sjoberg et al. 1990).



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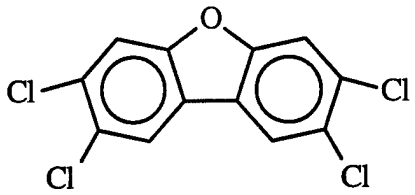

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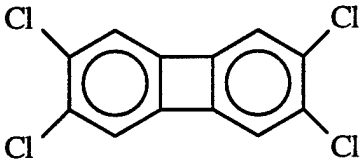

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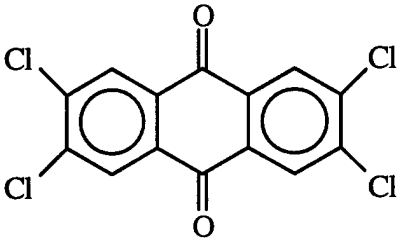

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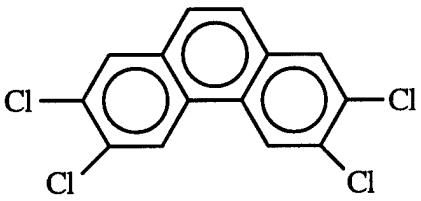

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Laboratory studies have reported an excellent correlation between the toxicities of the dibenzo-*p*-dioxins and related compounds and their abilities to induce aryl hydrocarbon hydroxylase (AHH) activity (Poland and Knutson 1982), suggesting that some mechanistic features may be common to both the toxic and AHH-inducing activities of these compounds. Indeed, both the toxicities and the

AHH-inducing activities of the dibenzo-*p*-dioxins have been found to correlate well with binding affinities to a cytosolic receptor (Poland, Greenlee and Kende 1979; Poland and Knutson 1982).

Certain structural features have been identified as being associated with high degrees of toxicity, AHH induction and receptor binding for the dibenzo-*p*-dioxins and related compounds (Poland and Knutson 1982). These are as follows:

(1) The molecules should be essentially planar and rectangular, with dimensions of roughly 3 x 10 Å.

(2) At least three of the four lateral positions (2,3,7,8; see **19**) should have halogen substituents.

(3) The activity induced by halogen substituents decreases in going from bromine to chlorine to fluorine.

(4) At least one ring position should remain unsubstituted.

Clearly, other molecular frameworks exist, besides dibenzo-*p*-dioxin, that can approximately meet the size and shape requirements, for example, **22** - **25**. These also have four lateral positions chlorinated. It is interesting to look at the levels of biological activity of these analogues, in comparison to TCDD. **22**, 2,3,7,8-tetrachlorodibenzofuran, and **23**, 2,3,6,7-tetrachlorobiphenylene, have activities that are, respectively, slightly less than and very similar to that of TCDD (Poland, Greenlee and Kende 1979; Poland and Knutson 1982). On the other hand, **24** and **25** are much less active than is TCDD.

We have shown that the biological activities of **22** - **25** can be understood in terms of the degree to which their electrostatic potentials mimic that of TCDD (Murray, Evans and Politzer 1990). Since a molecule encounters a receptor at some

distance from itself, the electrostatic potentials have been computed either in planes 1.75 Å above the framework of the molecule or on molecular surfaces. To provide a basis for understanding the potentials of TCDD and **22** - **25**, it is instructive to first consider that of the unsubstituted parent molecule dibenzo-*p*-dioxin, **20**. Its V(**r**) is weakly negative above the outer aromatic rings and strongly negative in the areas surrounding the oxygen atoms, while the potentials above the lateral regions are positive in sign (Murray et al. 1986; Sjoberg et al. 1990). The replacement of the lateral hydrogens by chlorines to give TCDD results in a complete transformation of the V(**r**) pattern. In TCDD, at 1.75 Å above the plane, there are no negative regions associated with either the aromatic rings or the central oxygens; however V(**r**) is now negative above the lateral positions (Murray et al. 1986).

The electrostatic potential of **22** is similar to that of TCDD, but lacks the horizontal plane of symmetry of the latter. An even closer match are the potentials of TCDD and **23**, which share the same degree of symmetry. The similarity in the biological activities of TCDD, **22** and **23** shows that the oxygens in TCDD and **22** are not necessary for high activity. In fact, they can even be an inhibiting influence, as is apparently the case for **24**, which has a potential pattern similar to that of TCDD but is much less active, presumably because the regions of negative potential near the central carbonyl oxygens in **24** are stronger than those in TCDD and **22**. V(**r**) for **25** also differs significantly from that of TCDD in that the negative regions of the "lateral" chlorines actually overlap on one side of the framework, so that there is not a true extended positive region separating them.

Our electrostatic potential analyses of TCDD, **22** - **25**, and a number of other dibenzo-*p*-dioxins have allowed us to make some generalizations about the

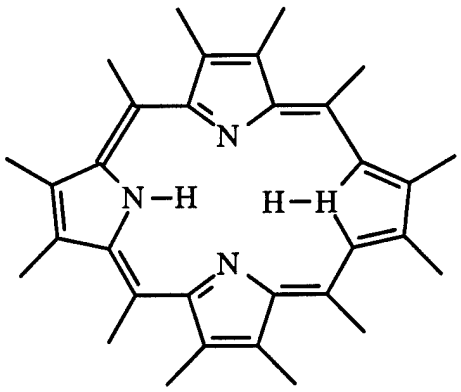
V(**r**) pattern that appears to lead to high biological activity for this class of halogenated aromatics. These are listed below:

(1) Biological activity appears to require negative potentials above all or most of the lateral positions, with optimum values of the minima, at 1.75 Å above the plane, being about –13 kcal/mole (at the STO-5G level) (Murray, Evans and Politzer 1990; Murray and Politzer 1987; Murray et al. 1986; Politzer 1988; Sjoberg et al. 1990).

(2) The negative regions of V(**r**) above the lateral positions of the molecule should be separated by a large central region of positive V(**r**).

(3) Negative regions of V(**r**) associated with central oxygens are not necessary for high activity; on the contrary, in systems that do have oxygens in or bonded to the center ring, it is important that the oxygen potentials be relatively weak and small (Murray, Evans and Politzer 1990; Murray and Politzer 1987; Politzer 1988; Sjoberg et al. 1990).

Although the actual structure of the receptor binding site is not known, some theoretical modeling computations based on experimental competitive binding studies support a stacking interaction model (Long, McKinney and Pedersen 1987; McKinney et al. 1985; McKinney, Long and Pederson 1984; McKinney and Pederson 1986). In this model, the toxigen is envisioned as being involved in a recognition step at a porphine-like binding site (**26**). For the specific case of TCDD, the most favorable interaction has been found to be one where the molecular planes of **19** and **26** are parallel to one another and separated by 3.38 Å (McKinney, Long and Pederson 1984), with the dioxin oxygens roughly above the unsubstituted nitrogens of **26**. It has been shown in previous work



26

(Politzer and Daiker 1981; Politzer and Murray 1990; Politzer and Murray 1991) that heterocyclic nitrogens, such as the doubly-coordinated ones in **26**, have large and strongly negative potentials associated with them. We have suggested that the observed need for small and weak negative oxygen potentials in the active dibenzo-*p*-dioxins, dibenzofurans, and other analogues containing central oxygens may be to avoid repulsive interactions with negative regions of $V(\mathbf{r})$ above the center of the receptor, e.g. the doubly-coordinated nitrogens in **26**.

This example of the electrostatic potentials of the dibenzo-*p*-dioxins shows how the patterns associated with high activity may be used to infer information about the actual receptor. The same approach can be used for other drug-receptor and toxigen-receptor systems.

C. Statistically-based Interaction Indices Derived from Electrostatic Potentials Computed on Molecular Surfaces: A General Interaction Properties Function (GIPF)

1. Background

In the preceding sections we have discussed how the electrostatic potential can be used successfully to study molecular phenomena involving noncovalent interactions. We have shown that the patterns of positive and negative $V(\mathbf{r})$ and the positions and values of $V(\mathbf{r})$ extrema can be useful in understanding and predicting the most favorable sites and orientations for noncovalent interactions, e.g. hydrogen or "halogen" bonding, and for interpreting the recognition of a molecule by a receptor.

In recent years, we have extended the nature of our analysis to include certain statistically-defined features of the surface electrostatic potential. Our purpose has been to expand the capabilities of $V(\mathbf{r})$ for quantitatively describing macroscopic properties that reflect noncovalent molecular interactions. This has led to the development of the General Interaction Properties Function (GIPF), described by eq. (7):

$$\text{Property} = f[\text{area}, V_{S,max}, V_{S,min}, \Pi, \sigma^2_{tot}, \nu] \tag{7}$$

The macroscopic property of interest, e.g. heat of vaporization, is represented in terms of some subset of the computed quantities on the right side of eq. (7). The latter are measures of various aspects of a molecule's interactive behavior, with all but surface area being defined in terms of the electrostatic potential computed on the molecular surface. $V_{S,max}$ and $V_{S,min}$, the most positive and most negative values of $V(\mathbf{r})$ on the surface, are site-specific; they indicate the tendencies and most

favorable locations for nucleophilic and electrophilic interactions. In contrast, Π, σ^2_{tot} and ν are statistically-based global quantities, which are defined in terms of the entire molecular surface. Π is a measure of local polarity, σ^2_{tot} indicates the degree of variability of the potential on the surface, and ν is a measure of the electrostatic "balance" between the positive and negative regions of $V(\mathbf{r})$ (Murray et al. 1994; Murray and Politzer 1994).

The macroscopic properties that have been represented successfully by variations of eq. (7) include boiling points (Murray et al. 1993a), critical constants (temperatures, pressures and volumes) (Murray et al. 1993a), partition coefficients (Brinck, Murray and Politzer 1993; Murray, Brinck and Politzer 1993), solubilities in supercritical fluids (Murray et al. 1993b; Politzer et al. 1992a; Politzer et al. 1993), heats of vaporization (Murray, Lane and Politzer 1995b; Murray and Politzer 1994), heats of sublimation (Politzer et al. 1997), heats of fusion (Murray, Brinck and Politzer 1996), liquid and crystal densities (Murray, Brinck and Politzer 1996), surface tension (Murray, Brinck and Politzer 1996), diffusion constants (Politzer, Murray and Flodmark 1996), C_{60} solubilities (Murray, Gagarin and Politzer 1995), and nitroaromatic and nitroheterocyclic impact sensitivities (Murray, Lane and Politzer 1995a). A key point to note is that liquid, solid and solution properties are being expressed solely in terms of quantities computed for individual molecules; environmental factors are not *explicitly* taken into account.

In this section, we will first define and discuss the global quantities Π, σ^2_{tot} and ν. This will be followed by a review of some earlier and current applications of this approach.

2. Methodology

The first step in our procedure is to compute an optimized structure for each molecule and then to use this geometry to compute the electronic density and the electrostatic potential. A large portion of our work in this area has been carried out at the SCF/STO-5G*// SCF/STO-3G* level, although some other basis sets have also been used. We then compute $V(\mathbf{r})$ on 0.28 bohr grids over molecular surfaces defined as the 0.001 au contour of the electronic density (Bader et al. 1987). The numbers of points on these grids are converted to surface areas ($Å^2$), and the $V_{S,max}$ and $V_{S,min}$ are determined. Our statistically-based interaction indices Π, σ^2_{tot} and ν are then calculated according to eqs. (8) - (10).

$$\Pi = \frac{1}{n}\sum_{i=1}^{n}\left|V(\mathbf{r}_i) - \overline{V}_S\right| \tag{8}$$

$$\sigma^2_{tot} = \sigma^2_+ + \sigma^2_- = \frac{1}{m}\sum_{i=1}^{m}\left[V^+(\mathbf{r}_i) - \overline{V}^+_S\right]^2 + \frac{1}{n}\sum_{j=1}^{n}\left[V^-(\mathbf{r}_j) - \overline{V}^-_S\right]^2 \tag{9}$$

$$\nu = \frac{\sigma^2_+\,\sigma^2_-}{\left[\sigma^2_{tot}\right]^2} \tag{10}$$

$V(\mathbf{r}_i)$ is the value of $V(\mathbf{r})$ at point $\mathbf{r}_i$ on the surface, and $\overline{V}_S$ is the average over the surface. Similarly, $V^+(\mathbf{r}_i)$ and $V^-(\mathbf{r}_i)$ are the positive and negative values of $V(\mathbf{r})$ on the surface, and $\overline{V}_{S^+}$ and $\overline{V}_{S^-}$ are the averages: $\overline{V}_{S^+} = \frac{1}{m}\sum_{i=1}^{m} V^+(\mathbf{r}_i)$ and $\overline{V}_{S^-} = \frac{1}{n}\sum_{j=1}^{n} V^-(\mathbf{r}_j)$.

Statistically, Π is the average deviation of $V(\mathbf{r})$ on the molecular surface; we view it as being indicative of the local polarity, or charge separation, that is present even in molecules having zero dipole moments (Brinck, Murray and Politzer 1992a), e.g. BF_3 and *p*-dinitrobenzene. We have shown that Π correlates in a general fashion with several empirical polarity scales and with the dielectric constant (Brinck, Murray and Politzer 1992a; Murray et al. 1994).

σ^2_{tot} is the total variance of $V(\mathbf{r})$ on the molecular surface, equal to the sum of the positive and negative variances, σ^2_+ and σ^2_-, which are calculated separately. It is a measure of the variability within the positive and negative regions of the surface potential; because the terms in eq. (9) are squared, σ^2_{tot} is particularly sensitive to the extremes of $V(\mathbf{r})$. We have found it to be an effective indicator of a molecule's overall tendency for noncovalent electrostatic interactions (Murray et al. 1994; Murray and Politzer 1994). In some instances it is preferable to use σ^2_+ or σ^2_- alone, instead of σ^2_{tot} (Brinck, Murray and Politzer 1993; Murray, Brinck and Politzer 1993; Politzer, Murray and Flodmark 1996). The former refer specifically to tendencies for nucleophilic and electrophilic noncovalent interactions, respectively.

The function of ν, defined by eq. (10), is to give the degree of balance between the positive and negative potentials on the surface (Murray et al. 1994; Murray et al. 1993a; Murray et al. 1993b). When σ^2_+ and σ^2_- are equal, ν attains a maximum value of 0.250; accordingly, the closer ν is to 0.250, the better able is the molecule to interact to a similar extent (whether strongly or weakly) through both its positive and negative potentials. Our most frequent use of ν has been as a factor in the product $\nu\sigma^2_{tot}$ (Murray et al. 1994; Murray, Brinck and Politzer 1996; Murray

et al. 1993a; Murray et al. 1993b; Murray, Lane and Politzer 1995b; Murray and Politzer 1994), which has been found to be a key term in representing properties that reflect the electrostatic interactions of a molecule with others of its own kind, e.g. boiling points and critical temperatures (Murray et al. 1993a), surface tension (Murray, Brinck and Politzer 1996), and heats of vaporization (Murray and Politzer 1994) and sublimation (Politzer et al. 1997).

For illustrative purposes, Table 3 gives Π, σ_+^2, σ_-^2, σ_{tot}^2, ν and $\nu\sigma_{tot}^2$ for thirty molecules of a variety of types. More complete compilations can be found elsewhere (Murray et al. 1994; Murray et al. 1993a; Murray and Politzer 1994). The molecules in Table 3 are listed in order of increasing Π. It should be noted that some of the larger Π values are for molecules having zero dipole moments but nevertheless considerable internal charge separation, e.g. perfluorobenzene and 1,3,5-trinitrobenzene. Although Π and σ_{tot}^2 may seem to be measuring similar effects, the data in Table 3 clearly show that these are quite different quantities. Π covers a range from 2 to 20 kcal/mole for most organic molecules, while σ_{tot}^2 ranges from 3 to over 300 (kcal/mole)^2 (Murray et al. 1994); more important, they do not necessarily vary in the same direction. For the molecules in Table 3, the linear correlation coefficient between Π and σ_{tot}^2 is only 0.721.

It is interesting to look at the relative magnitudes of σ_+^2 and σ_-^2 in relation to the known interactive behavior of some of the molecules. For example, the σ_+^2 values for diethyl ether, pyridine and acetone are low, all under 20 (kcal/mole)^2, while σ_-^2 for these three molecules is in each case over 125 (kcal/mole)^2. Diethyl ether, pyridine and acetone are all known to be good hydrogen bond acceptors, but not good hydrogen bond donors. Our $V(\mathbf{r})$ results would predict this behavior.

Table 3. Calculated global properties and experimentally-derived Hildebrand parameters (δ) for a group of organic molecules.

Molecule	Π	σ_+^2	σ_-^2	σ_{tot}^2	ν	$\nu\sigma_{tot}^2$	δ
cyclohexane	2.16	2.5	0.7	3.2	0.171	0.55	16.8
n-octane	2.32	2.6	1.0	3.6	0.201	0.72	15.3
n-hexane	2.33	2.7	0.9	3.6	0.188	0.68	14.9
n-pentane	2.35	2.8	0.9	3.6	0.194	0.70	14.5
1,3-butadiene	4.50	7.6	7.5	15.1	0.250	3.78	14.5
toluene	4.63	6.8	11.1	17.9	0.236	4.22	18.2
benzene	4.83	7.1	9.2	16.3	0.246	4.01	18.8
naphthalene	5.12	8.1	7.8	15.9	0.250	3.98	20.3
carbon tetrachloride	5.22	28.8	2.5	31.3	0.073	2.28	17.6
phenanthrene	5.28	9.7	7.1	16.8	0.244	4.10	20.0
anthracene	5.30	8.8	6.8	15.6	0.246	3.84	20.3
diethyl ether	6.68	8.0	129.8	137.8	0.055	7.58	15.1
chloroform	7.54	53.5	7.4	60.9	0.107	6.52	18.8
1-butanol	7.54	35.0	165.9	201.0	0.144	28.94	23.1
pyridine	8.55	18.5	212.3	230.8	0.074	17.08	21.7
2-propanol	8.70	35.5	184.2	219.7	0.135	29.66	24.5
chloroethane	9.00	14.3	28.4	42.7	0.223	9.52	17.0
acetone	9.40	15.9	159.8	175.7	0.082	14.41	20.0

(continued)

Table 3. Calculated global properties and experimentally-derived Hildebrand parameters (δ) for a group of organic molecules (continued).

Molecule	Π	σ_+^2	σ_-^2	σ_{tot}^2	ν	$\nu\sigma_{tot}^2$	δ
dichloro-methane	9.66	46.3	13.8	60.1	0.177	10.64	20.0
ethanol	10.05	45.1	182.4	227.5	0.159	36.17	26.4
perfluoro-benzene	10.35	39.1	6.1	45.3	0.116	5.25	---
N,N-dimethyl formamide	11.07	18.6	158.8	177.4	0.094	16.68	24.8
iodoform	12.02	20.3	24.0	44.3	0.248	10.99	20.3
nitrobenzene	12.13	16.7	105.2	121.9	0.118	14.38	21.7
methanol	12.79	49.6	181.5	231.0	0.169	39.04	29.2
dimethyl-sulfoxide	15.39	24.3	271.7	296.0	0.075	22.20	26.4
acetonitrile	17.12	23.6	167.8	191.4	0.108	20.67	24.0
formamide	17.31	85.5	233.6	319.1	0.196	62.54	36.4
1,3,5-trinitro-benzene	18.70	105.3	47.4	152.7	0.214	32.68	---
nitromethane	19.90	34.4	81.7	116.0	0.209	24.24	25.2

Units are: kcal/mole for Π; $(\text{kcal/mole})^2$ for σ_+^2, σ_-^2, σ_{tot}^2 and $\nu\sigma_{tot}^2$; $MPa^{1/2}$ for δ.

These σ_+^2 and σ_-^2 values are reflected in the electrostatic balance term ν, which is between 0.05 and 0.08 for these molecules. Examples of molecules with ν

approaching the limit of 0.250 are the aromatics in Table 3. The latter interact to a similar degree through both their positive and negative regions of $V(\mathbf{r})$. The molecule with the highest value of σ^2_{tot} in Table 3 is formamide, which also has a relatively high ν. This combination yields the largest $\nu\sigma^2_{tot}$ in Table 3.

Figure 4 shows a fair correlation between $\nu\sigma^2_{tot}$ and the Hildebrand solubility parameter δ (linear correlation coefficient = 0.930) which makes intuitive sense. The Hildebrand parameter, which is often used to characterize liquids, is defined as the square root of the cohesive energy density (Barton 1991), while $\nu\sigma^2_{tot}$ can be viewed as reflecting how strongly a molecule interacts with others of the same kind (Murray et al. 1994).

3. Applications of GIPF

Table 4 presents our GIPF relationships for some properties that can be regarded as involving noncovalent interactions. The equations for the properties that are characteristic of pure compounds (normal boiling point, critical temperature, volume and pressure, heat of vaporization, and surface tension) invariably include area in some form and nearly always (critical volume being an exception) also a term containing $\nu\sigma^2_{tot}$. As we have mentioned earlier, the latter has emerged as being important for properties that are determined by how well a molecule interacts with its own kind. For example, $\nu\sigma^2_{tot}$ for 1-butanol is greater than that of diethyl ether [28.94 vs. 7.5 $(kcal/mole)^2$], largely because of their relative ν values, 0.144 and 0.055. These reflect the greater ability of 1-butanol to interact through both its positive and negative regions, while diethyl ether is primarily limited to its negative $V(\mathbf{r})$. The case of diethyl ether is typical of other compounds which operate as hydrogen bond acceptors but not as donors; although $(C_2H_5)_2O$ has a strong

negative potential near its oxygen, this does not promote highly favorable interactions with other molecules of the same kind because their positive potentials are so weak. To show how these factors affect a physical property, the normal boiling points of 1-butanol and diethyl ether are 390 and 308 K, respectively.

Also in Table 4 are some solubility relationships (including partition coefficients) and one transport property. In these cases, the molecule in question is interacting with other kinds, and the product $\nu\sigma_{tot}^2$ is found to be of less importance. Instead, σ_{tot}^2, σ_+^2 and σ_-^2 often appear in the equations, along with terms involving molecular size.

V. Summary

The use of the electrostatic potential in analyzing and predicting molecular interactive behavior and properties has increased remarkably over the past 25 years. In 1980, it was still reasonable to hope to at least mention, in one lengthy review chapter (Politzer and Daiker 1981), all of the papers that had been published in this area. In 1996, such an objective would be ridiculous. This popularity can be

Table 4. Some GIPF relationships.[a,b]

Relationship[c]	N	R	S. D.	Ref.
Normal boiling point, T_{bp}:				
$T_{bp} = \alpha(\text{area}) + \beta(\nu\sigma_{tot}^2)^{0.5} - \gamma$	100	0.948	37.0	158
Heat of vaporization, $\Delta\overline{H}_v$:				
$\Delta\overline{H}_v = \alpha(\text{area})^{0.5} + \beta(\nu\sigma_{tot}^2)^{0.5} - \gamma$	40	0.971	2.03	25
Critical temperature, T_c:				
$T_c = \alpha(\text{area})^{0.5} + \beta(\nu\sigma_{tot}^2)^{0.25} - \gamma$	66	0.909	60.7	158
Critical volume, $\overline{V}_c$:				
$\overline{V}_c = \alpha(\text{area})^{1.5} + \beta$	58	0.986	15.2	158
Critical pressure, P_c:				
$P_c = -\alpha(\text{area}) + \beta(\nu\sigma_{tot}^2 / \text{area}) + \gamma$	57	0.910	4.8	158
Octanol/water partition coefficient, P_{ow}:				
$\log P_{ow} = \alpha(\text{area}) - \beta(\sigma_-^2) - \gamma(\text{area})\Pi - \varepsilon$	70	0.961	0.437	158
Solubility in supercritical CO_2 at 14 MPa and 308 K:				
$\ln(\text{sol}) = \alpha(\text{vol})^{-1.5} - \beta(\sigma_{tot}^2)^2 - \gamma$	21	0.95		162
Solubility of C_{60} in organic solvents: $\log(\text{sol} \times 10^4) =$ $-\alpha\left[\frac{\sigma_{tot}^2}{(\text{area})^{3/2}}\right] + \beta(\nu\sigma_{tot}^2)^{1/2} + \gamma(\text{area})^4 - \varepsilon$	20	0.954	0.475	167

(continued)

Table 4. Some GIPF relationships (continued).[a,b]

Relationship[c]	N	R	S. D.	Ref.
Surface tension, γ; $\gamma = \alpha(\text{area})^{1/4} + \beta\left(\Pi^2/_{\text{area}}\right) + \gamma(\nu\sigma^2_{\text{tot}})^{3/2} - \varepsilon$	26	0.923	4.75	165
Diffusion constants of developing agents, D; in dry gelatin: $Dx10^7 = \alpha(\text{area})^{-1} - \beta\sigma^2_+ + \gamma\sigma^2_- - \varepsilon$	10	0.990	0.09	166

[a]N is number of systems in data base; R is correlation coefficient; S. D. is standard deviation. [b]Units: T_{bp}, K; T_c, K; $\overline{V}_c$, cm^3/mole; P_c, bar; $\Delta\overline{H}_v$, kJ/mole; γ, dyn/cm; D, cm^2/sec. [c]All coefficients (α, β, γ, ε, η) are positive numbers.

attributed to (a) the insight that $V(\mathbf{r})$ can provide, especially into noncovalent interactions, and (b) the widespread availability of computational software packages of which it has become a standard feature.

In this chapter, we have sought to convey some appreciation of the sort of questions that can and have been addressed by means of the electrostatic potential, and further to indicate some possible future directions. In particular, we believe that quantities derived from $V(\mathbf{r})$, such as Π and σ^2_{tot}, will find increasing application in quantitatively describing macroscopic properties based on noncovalent interactions. Biological systems should provide some fruitful areas for exploration, e.g. drug-receptor binding constants. Overall, a continuing extensive use of the electrostatic potential to analyze an expanding array of phenomena can be anticipated.

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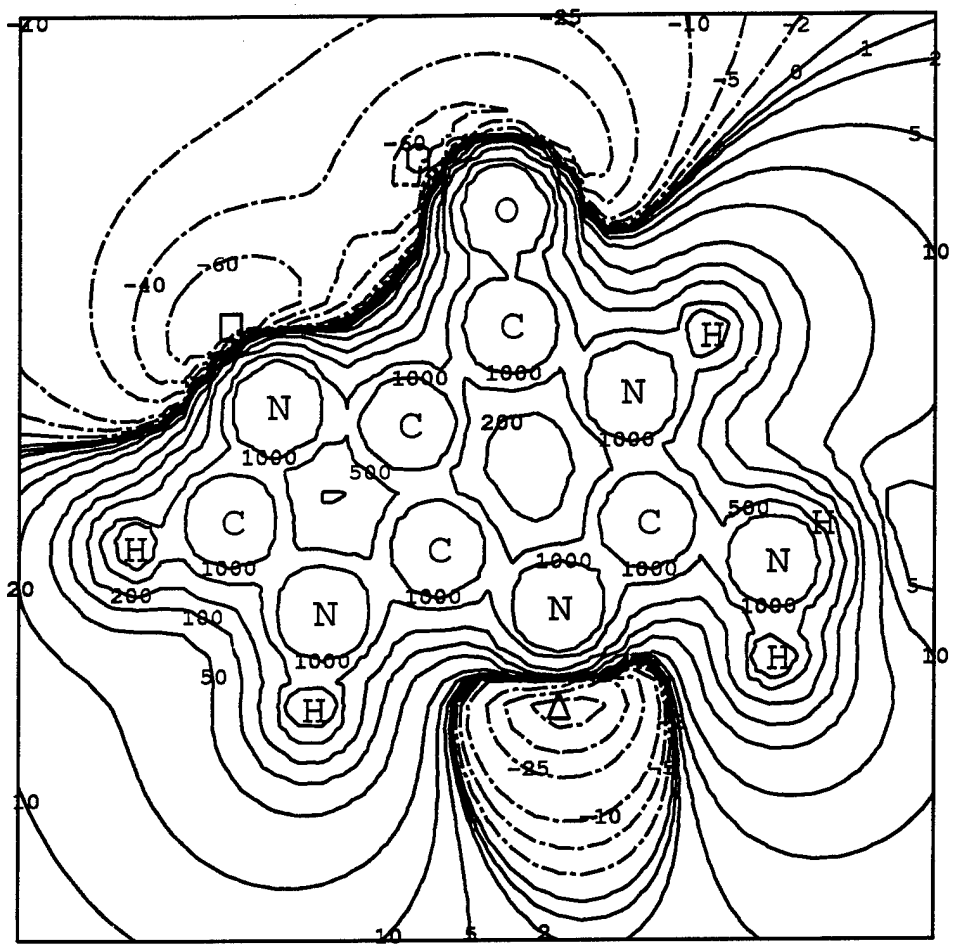
FIGURE CAPTIONS

Figure 1. Calculated electrostatic potential of guanine (**1**), in kcal/mole, in the plane of the molecular framework. Dashed contours correspond to negative potentials. The positions of the most negative potentials are indicated; the values are: □ -92.6; Δ -72.6; ○ -69.2.

Figure 2. Calculated electrostatic potential on the molecular surface of guanine (**1**). Three ranges of V(**r**) are depicted, in kcal/mole. These are: white for V(**r**) < 0; light gray for V(**r**) from 0 to 10; dark gray for V(**r**) > 10.

Figure 3. Calculated electrostatic potential on the molecular surface of 1,3-bisdiphenylurea (**13**). Three ranges of V(**r**) are depicted, in kcal/mole. These are: white for V(**r**) < 0; light gray for V(**r**) from 0 to 10; dark gray for V(**r**) > 10.

Figure 4. Plot of calculated $\nu\sigma_{tot}^2$ values, (in kcal/mole)^2, versus Hildebrand solubility parameters δ, in MPa$^{1/2}$, for the molecules given in Table 3. The linear correlation coefficient and standard deviation are 0.930 and 1.9 MPa$^{1/2}$, respectively.



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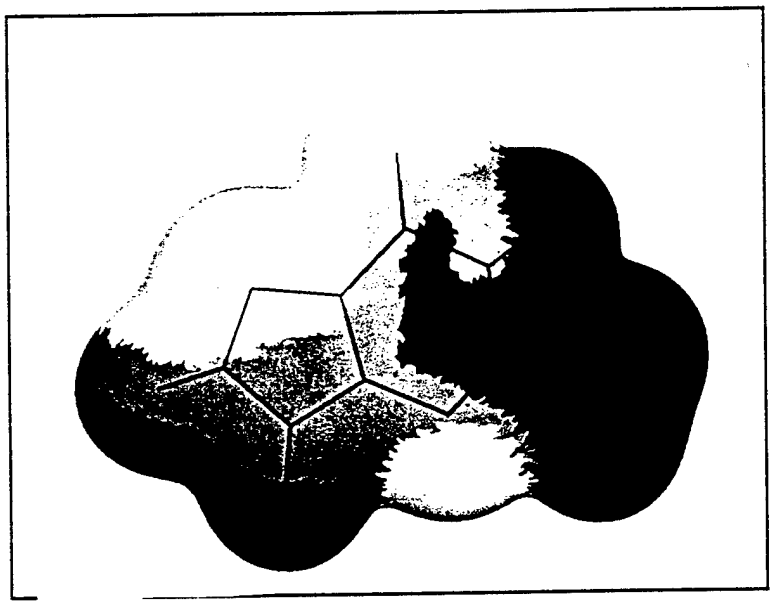

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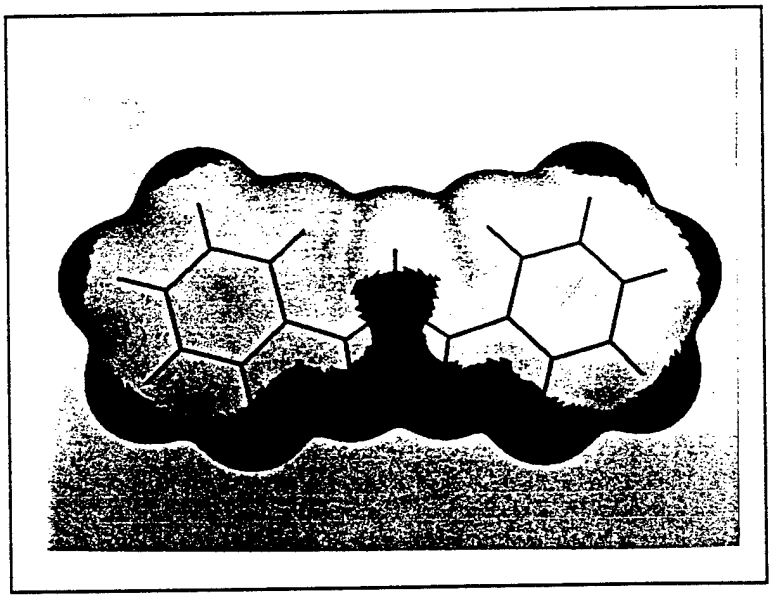

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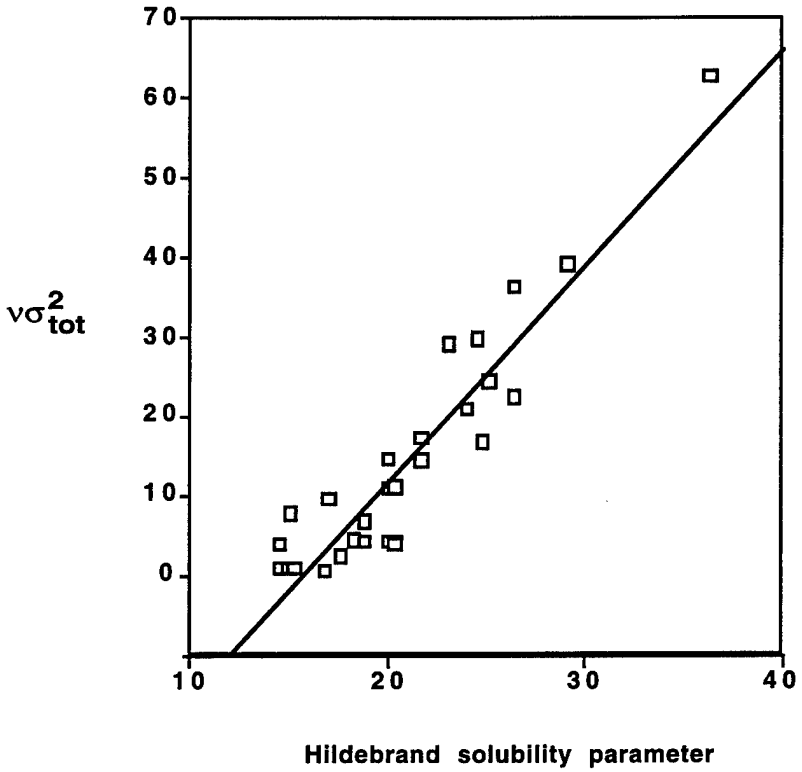

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