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The fundamental nature and role of the electrostatic potential in atoms and molecules

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Abstract. A variety of atomic and molecular properties can be expressed in terms of the electrostatic potential. These include energies, covalent and anionic radii, electronegativities (chemical potentials) and a variety of properties that depend upon noncovalent interactons. We present a survey of such relationships, which may be exact or approximate; they may involve the potential in three-dimensional space, along the axes between bonded atoms, at nuclei or on molecular surfaces. Thus, the electrostatic potential, which is rigorously related to the electronic density by Poisson's equation, can be regarded as, effectively, another fundamental determinant of atomic and molecular properties.

Key words: Electrostatic potentials – Energies – Covalent and anionic radii – Electronegativities – Noncovalent interactions

1 The electronic density and the electrostatic potential

The remarkable and extremely important Hohenberg–Kohn theorem established that the properties of a ground-state system of electrons and nuclei are determined, rigorously and completely, by the electronic density, $\rho(\mathbf{r})$ [1]. For example, the total energy can be expressed as the functional

$$E = f[\rho(\mathbf{r})] \ . \tag{1}$$

Thus the theorem focuses attention upon the electronic density, a physical observable, rather than the wave function, a mathematical construct.

The Hohenberg–Kohn theorem has led to very significant advances, both conceptual and computational. Parr, Levy and their colleagues have made notable progress in developing the theory and its relevance to chemistry [2, 3, 4, 5, 6]; meanwhile the Kohn–Sham formalism [7], as extended by Perdew, Becke and others [3, 4, 6, 8], has provided the basis for accurate calculations of electronic and molecular properties of relatively large systems, including correlation effects, at a cost in computer resources comparable to that of Hartree–Fock methodology.

The central role of the electronic density has further been emphasized by Bader and his colleagues, in their mathematically elegant theory of "atoms in molecules" [9]. However, $\rho(\mathbf{r})$ does not always lend itself to further analytical development. For example, the exact form of Eq. (1) remains unknown, notwithstanding the very effective approximations that have emerged [3, 4, 6, 8]. Galvez and Porras [10] observed, with respect to the electronic density of an atom, "It is hard to prove mathematical properties of this quantity in a rigorous way."

Poisson's equation relates the electronic density to the electrostatic potential, V(**r**), that is created by the nuclei and electrons of the system [11]:

$$\nabla^2 V(\mathbf{r}) = 4\pi\rho(\mathbf{r}) - 4\pi\sum_{\mathrm{A}} Z_{\mathrm{A}}\delta(\mathbf{r} - \mathbf{R}_{\mathrm{A}}) \ . \tag{2}$$

Z_{A} is the charge on nucleus A, located at $\mathbf{R}_{\mathrm{A}}$. $V(\mathbf{r})$ is given by Eq. (3), which is simply an expression of Coulomb's law:

$$V(\mathbf{r}) = \sum_{\mathrm{A}} \frac{Z_{\mathrm{A}}}{|\mathbf{R}_{\mathrm{A}} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\mathrm{d}\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \ . \tag{3}$$

In view of the link between $V(\mathbf{r})$ and $\rho(\mathbf{r})$ that is indicated in Eq. (2), suggest that the electrostatic potential can also be regarded as a fundamental quantity, in terms of which some analyses may be facilitated. For example, while it has been shown empirically that $\rho(\mathbf{r})$ decreases monotonically with radial distance from the nucleus for ground-state neutral atoms, proving this mathematically continues to be a challenge [12, 13, 14, 15, 16, 17]. In contrast, this was established very easily for $V(\mathbf{r})$ [13] by means of Poisson's equation.

We shall focus upon the electrostatic potential as a determinant of atomic and molecular properties and

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reactive behavior. Our discussion will be on both exact and approximate levels. For an earlier survey of some of these topics, see Ref. [18].

2 Topography of $V(\mathbf{r})$

2.1 General

Equation (3) shows that the sign of the electrostatic potential at any point in the space of an atom or molecule depends upon whether the positive nuclear contribution or the negative one of the electrons is dominant there. In the case of a neutral, spherically-averaged ground-state atom or positive monatomic ion, $V(\mathbf{r})$ is positive everywhere and goes down monotonically from the nucleus to zero at infinity [13, 19]. For a negative monatomic ion, $V(\mathbf{r})$ is positive near the nucleus but then decreases to a negative minimum at a radial distance r_m, after which it approaches zero at infinity. At the minimum, the encompassed electronic charge exactly equals the nuclear charge [19], which is accordingly fully shielded; thus the negative potential at r_m is due entirely to the excess electronic charge of the ion. This potential determines the strengths of its interactions with other ions. We have shown that the radial distances to the minima provide good estimates of crystallographic ionic radii [19, 20], and that the magnitudes of $V(r_m)$ correlate well with lattice energies, for a given positive ion.

The isopotential surface $V(r_m)$ characterizes, therefore, a monatomic negative ion. Gadre and Shrivastava [21] have extended this concept to polyatomic anions, defining their boundary surfaces by the condition $\nabla V(\mathbf{r})\cdot\mathbf{s}(\mathbf{r}) = 0$, where $\mathbf{s}(\mathbf{r})$ is a unit vector perpendicular to the surface at $\mathbf{r}$.

While the electrostatic potential is positive everywhere for neutral atoms, their interaction to form molecules is accompanied by subtle but very important rearrangements of electronic charge that normally produce some regions of negative $V(\mathbf{r})$ in the molecule [22, 23, 24, 26, 26]. These are typically associated with the lone pairs of the more electronegative atoms (e.g. N, O, F, Cl, etc.), the π electrons of unsaturated hydrocarbons and strained C–C bonds. Each such region necessarily has one or more local minima, $V_{\min}$ [points at which $V(\mathbf{r})$ reaches its most negative values]. In the past, these have often been used to identify and rank sites susceptible to electrophilic attack [22, 23, 24, 25, 26]; this shall be discussed further in a later section. It has been shown by Pathak and Gadre [27], however, that there are no local maxima other than at the positions of the nuclei. Thus, $V(\mathbf{r})$ decreases monotonically from each nucleus to the local minima, which are separated by saddle points. The topographical properties of molecular electrostatic potentials have been studied extensively by Gadre and coworkers [21, 27, 28, 29, 30, 31], both in the gas phase and in aqueous solution.

2.2 Covalent radii

It has long been recognized that atoms can be assigned "covalent radii," which can then be used to make reasonable predictions of actual bond lengths in a variety of molecules [32, 33, 34, 35, 36, 37, 38], either by direct summation or by invoking some empirical relationship. A number of different approaches have been utilized to obtain covalent radii, frequently involving some manner of apportioning the experimentally determined distances between bonded atoms in molecules and crystals. Several sets of values, taken from the literature, are given in Table 1. For the most part, they are in fairly satisfactory agreement, although there are some notable exceptions, for example, fluorine.

It is clear from the discussion in the preceding section that the electrostatic potential along the internuclear axis between two bonded atoms must reach an axial minimum (usually positive [34]) at some intermediate point $\mathbf{r}_m$. Then $\nabla V(\mathbf{r}_m)\cdot\mathbf{u} = 0$, where $\mathbf{u}$ is a unit vector along the internuclear axis. It follows that an element of charge, δq, placed at the point $\mathbf{r}_m$ feels zero electrostatic force from either direction along the axis. Thus, $\mathbf{r}_m$ appears to

Table 1. Covalent radii (Å)

Atom	Literature values			Distances to axial minima[a,b]		Distances to $V(\mathbf{r}) = I$[c]
	Pauling[d]	O'Keeffe–Brese[e]	Huheey et al.[f]	$V(\mathbf{r})$	$\rho(\mathbf{r})$	
H	0.30	0.38	0.37	0.42 (0.05)	0.47 (0.20)	0.40[g]
C	0.772	0.78	0.77	0.76 (0.05)	0.68 (0.19)	0.78
N	0.70	0.72	0.75	0.72 (0.04)	0.79 (0.20)	0.68
O	0.66	0.63	0.73	0.68 (0.03)	0.88 (0.06)	0.66
F	0.64	0.58	0.71	0.70 (0.02)	0.89 (0.09)	0.59
Si	1.17	1.12	1.18	1.05 (0.04)	0.74 (0.02)	1.13
P	1.10	1.09	1.10	1.01 (0.04)	0.73 (0.03)	1.01
S	1.04	1.03	1.02	0.97 (0.04)	0.84 (0.11)	0.99
Cl	0.99	0.99	0.99	1.00 (0.02)	1.18 (0.16)	0.90

[a] Calculated distances taken from Ref. [40]

[b] Standard deviations from average values are given in parentheses

[c] Ref. [53]

[d] Ref. [34]

[e] Ref. [37]

[f] Ref. [38]

[g] Calculated using exact wave function

be a natural axial boundary point between the two atoms and could be used to obtain their covalent radii.

We tested this idea for a group of representative molecules, containing nine different atoms [40]. $V(\mathbf{r})$ was computed at the density functional BLYP/6-31G** level (Becke exchange [41] and Lee–Yang–Parr correlation functionals [42]). For 19 bonds in these molecules, we found the distance from each nucleus to the axial minimum of $V(\mathbf{r})$. The average values of these distances are listed in Table 1. Also included are the averaged distances to the axial minima of $\rho(\mathbf{r})$, since Bader and coworkers [9, 43, 44, 45] have argued that the condition $\nabla\rho(\mathbf{r})\cdot\mathbf{s}(\mathbf{r}) = 0$ defines the boundary surface of an atom in a molecule.

The first point to note in Table 1 is that the distances to the axial minima of $V(\mathbf{r})$ fluctuate relatively little, much less that do their $\rho(\mathbf{r})$ counterparts; the largest standard deviations for the former are 0.05, while the latter have three in the neighborhood of 0.20 and two more that are 0.10 or more. Second, the distances to the $V(\mathbf{r})$ axial minima are overall in reasonable agreement with the various covalent radii reported in the literature, much more so than are those corresponding to the $\rho(\mathbf{r})$ minima; overall, the contrast is quite striking! For example, the $\rho(\mathbf{r})$ results imply that the sizes of the atoms increase considerably from carbon to fluorine and phosphorus to chlorine, and decrease from nitrogen to phosphorus and oxygen to sulfur, all of which is contrary to accepted chemical knowledge.

Digressing briefly, it is relevant to mention that atomic charges determined on the basis of the $\nabla\rho(\mathbf{r})\cdot\mathbf{s}(\mathbf{r}) = 0$ condition [9, 43] are also unrealistic in many instances; for a detailed analysis, see Ref. [46]. Indeed a seemingly more defensible approach to determining atomic charges, which is increasingly being applied, is by least-squares fitting to the molecular electrostatic potential [24, 47, 48, 49, 50].

Returning to covalent radii, the evidence that has been presented indicates that the minimum of $V(\mathbf{r})$ along the internuclear axis does represent a physically meaningful boundary point between two bonded atoms. In our earlier study, we also showed that the two atoms contribute approximately equally to the magnitude of $V(\mathbf{r})$ at its axial minimum [40]. This may help to explain some interesting observations related to covalent radii which, rather surprisingly, involve the electrostatic potentials of free atoms. It was found by Politzer et al. [50, 51] that the radial distance at which $V(\mathbf{r})$ equals the atom's chemical potential, μ, is a fair approximation to its covalent radius. The chemical potential was taken to be $\mu = 0.5(I + A)$, where I and A are, respectively, the ground-state ionization potential and electron affinity of the atom [52]. Later, however, it was shown that the points where $V(\mathbf{r}) = I$ are in significantly closer agreement with covalent radii reported in the literature [37, 53]. Some results are given in Table 1 [53], obtained using Clementi and Roetti's extended-basis-set Hartree–Fock wave functions to calculate $V(\mathbf{r})$ [54]. The success of the $V(\mathbf{r}) = I$ criterion can be rationalized by arguing that at the covalent radius of an atom X bonded to an atom Y, a valence electron on X should interact roughly equally strongly with both nuclei; this requires that, at this point, $I_X \approx V_Y(\mathbf{r})$. However, if the covalent radius corresponds to the axial minimum of the molecular $V(\mathbf{r})$, at which we have shown that $V_X(\mathbf{r}) \approx V_Y(\mathbf{r})$, then it is also characterized by $I_X \approx V_X(\mathbf{r})$. This interpretation is supported by the general similarity between the covalent radii resulting from these two independent approaches (Table 1), which might even increase if a larger database were used for finding the average distances to the $V(\mathbf{r})$ axial minima. This is being investigated. The particular significance of the $V(\mathbf{r}) = I$ condition yielding a reasonable estimate of the covalent radius is the implication that the latter is an intrinsic property of the isolated atom, whereas it is usually perceived in the context of bonding to other atoms.

3 Atomic and molecular energies

3.1 Exact relationships

It was pointed out in Sect. 1 that while the Hohenberg–Kohn theorem guarantees that the energy of a ground-state system of electrons and nuclei is a functional of the electronic density [1], Eq. (1), the exact form of that relationship has not been established [2, 3, 4, 5, 6, 7, 8]. In contrast, rigorous expressions have been derived for the energies of atoms and molecules in terms of their electrostatic potentials, specifically at their nuclei.

The starting point is the Hellman–Feynman theorem [55, 56], from which the following expression can be obtained, for atoms [57, 58, 59, 60]:

$$\left(\frac{\partial E^{\mathrm{at}}}{\partial Z}\right)_N = V_0 \ , \tag{4}$$

where V_0 is the electrostatic potential at the nucleus of an N-electron atom having nuclear charge Z and energy E^{at}; from Eq. (3), V_0 is given by

$$V_0 = -\int \frac{\rho(\mathbf{r})\mathrm{d}\mathbf{r}}{\mathbf{r}} \ . \tag{5}$$

The molecular equivalent of Eq. (4) is [61]

$$\left(\frac{\partial E^{\mathrm{mol}}}{\partial Z_{\mathrm{A}}}\right)_{N, Z_{\mathrm{B}\neq\mathrm{A}}} = V_{0,\mathrm{A}} \ , \tag{6}$$

where $V_{0,\mathrm{A}}$ is the electrostatic potential at nucleus A, having charge Z_{A} and located at $\mathbf{R}_{\mathrm{A}}$:

$$V_{0,\mathrm{A}} = \sum_{\mathrm{B}\neq\mathrm{A}} \frac{Z_{\mathrm{B}}}{|\mathbf{R}_{\mathrm{B}} - \mathbf{R}_{\mathrm{A}}|} - \int \frac{\rho(\mathbf{r})\mathrm{d}\mathbf{r}}{|\mathbf{r} - \mathbf{R}_{\mathrm{A}}|} \ . \tag{7}$$

Integration of Eqs. (4) and (6) should yield formulas for atomic and molecular energies in terms of electrostatic potentials at nuclei and nuclear charges. This was done by Foldy [57] for atoms and Wilson [61] for molecules, and both results were subsequently extended by Politzer and Parr [62] to produce

$$E^{\mathrm{at}} = \frac{1}{2} Z V_0 - \frac{1}{2} \int_0^Z \left[Z' \left(\frac{\partial V_0}{\partial Z'}\right) - V_0 \right]_N \mathrm{d}Z' \ . \tag{8}$$

and

$$E^{\mathrm{mol}} = \frac{1}{2}\sum_{\mathrm{A}} Z_{\mathrm{A}} V_{0,\mathrm{A}} - \frac{1}{2}\sum_{\mathrm{A}} \int_0^{Z_{\mathrm{A}}} \left[Z'_{\mathrm{A}} \left(\frac{\partial V_{0,\mathrm{A}}}{\partial Z'_{\mathrm{A}}} \right) - V_{0,\mathrm{A}} \right]_N \mathrm{d}Z'_{\mathrm{A}} \ . \tag{9}$$

Equations (8) and (9) are exact. A striking feature is that the molecular expression is simply a summation of its atomic counterparts for the constituent atoms; there are no explicit interaction or "mixing" terms. This certainly supports the concept of "atoms in molecules". (Alternative forms of Eqs. 8 and 9, having the same key properties, have recently been presented by Politzer [63].)

A second very interesting point can be brought out by applying the virial theorem [64]:

$$E^{\mathrm{at}} = 0.5(V_{\mathrm{ne}} + V_{\mathrm{ee}}) \ , \tag{10}$$

$$E^{\mathrm{mol}} = 0.5(V_{\mathrm{ne}} + V_{\mathrm{ee}} + V_{\mathrm{nn}}) \ , \tag{11}$$

where V_{ee}, V_{nn} and V_{ne} are, respectively, the electronic, nuclear and nuclear–electronic interaction energies. Looking at the first term on the right side of Eq. (8), it is clear that

$$ZV_0 = V_{\mathrm{ne}} \ , \tag{12}$$

while in Eq. (9)

$$\sum_{\mathrm{A}} Z_{\mathrm{A}} V_{0,\mathrm{A}} = V_{\mathrm{ne}} + 2V_{\mathrm{nn}} \ . \tag{13}$$

It follows then from the virial theorem that the integral terms in Eqs. (8) and (9) can be written as

$$-\int_0^{Z} \left[Z' \left(\frac{\partial V_0}{\partial Z'} \right) - V_0 \right]_N \mathrm{d}Z' = V_{\mathrm{ee}} \tag{14}$$

and

$$-\sum_{\mathrm{A}} \int_0^{Z_{\mathrm{A}}} \left[Z'_{\mathrm{A}} \left(\frac{\partial V_{0,\mathrm{A}}}{\partial Z'_{\mathrm{A}}} \right) - V_{0,\mathrm{A}} \right]_N \mathrm{d}Z'_{\mathrm{A}} = V_{\mathrm{ee}} - V_{\mathrm{nn}} \ . \tag{15}$$

In Eqs. (14) and (15), the electronic interaction energies, which are two-electron properties, are expressed rigorously in terms of electrostatic potentials at nuclei, which are one-electron properties. This can be viewed as a manifestation of the Hohenberg–Kohn theorem [1].

While the evaluation of the integrals in Eqs. (8) and (9) clearly poses problems, the conceptual significance of these relationships is in showing that exact atomic and molecular energies can be obtained without explicitly treating electronic interactions. It is easier to achieve good estimates of V_0 and $V_{0,\mathrm{A}}$ than of V_{ee}. For example, it is known that Hartree–Fock V_0 and $V_{0,\mathrm{A}}$ are correct through second order [65, 66]; i.e. the errors are third- and higher-order effects. Thus, for the atoms from Li to Cl, we found that the Hartree–Fock $V_{\mathrm{ne}}(=ZV_0)$ differ from the predicted exact (nonrelativistic) values (taken from Wang and Smith [67]) by an average of 0.184 hartrees [68], whereas the Hartree–Fock energies deviate by an average 0.347 hartrees. Since it is actually $0.5V_{\mathrm{ne}}$ that enters the atomic energy expression, Eq. (8), it follows that the error in E^{at} is 4 times as large as that in the term involving V_0. This means that inserting Hartree–Fock V_0 in Eq. (8) or a sufficiently accurate approximate E^{at}–V_0 relationship can be expected to lead to atomic energies that are better than the Hartree–Fock E^{at}. The same should be true of $V_{0,\mathrm{A}}$ and E^{mol}. This is indeed the case, as mentioned further in Sect. 3.2.

3.2 Approximate relationships

The integrals in Eqs. (8) and (9) would be more tractable if they were not restricted to isoelectronic sequences [66]. It has been shown that this requirement can be eliminated by introducing the assumptions [69]

$$\left(\frac{\partial E^{\mathrm{at}}}{\partial N} \right)_Z = 0 \tag{16}$$

and

$$\left(\frac{\partial E^{\mathrm{mol}}}{\partial N} \right)_{v(\mathbf{r})} = 0 \tag{17}$$

into the derivations of Eqs. (8) and (9), respectively. (In Eq. 17, $v(\mathbf{r})$ represents the electrostatic potential due to the nuclei of the molecule.) Equations (16) and (17) are equivalent to saying that the chemical potentials of the systems, μ^{at} and μ^{mol}, are zero [52]. Under these conditions, the isoelectronic restriction is removed and the integrations in Eqs. (8) and (9) can be carried out over any more convenient pathway. An obvious choice is a series of neutral atoms or molecules. Both have in fact been investigated; the average error for 13 atoms ($5 \le Z \le 17$) was 0.8% [62], while for eight first-row homo- and heteronuclear diatomic molecules it was 0.4% [69].

Within the framework of Thomas–Fermi theory [70, 71, 72, 73], a forerunner on an approximate level of the rigorous density functional theory represented by the Hohenberg–Kohn theorem [1, 2, 3, 4, 5, 6], all neutral atoms and molecules do have zero chemical potentials, i.e. Eqs. (16) and (17) are obeyed. Lieb and Simon [74, 75] have shown that the Thomas–Fermi theory becomes exact (in a relative sense) as the sum of the nuclear charges in a system approaches infinity; thus, it may be that the inaccuracy associated with using nonisoelectronic integration pathways in Eqs. (8) and (9) will diminish for large molecules.

In Thomas–Fermi theory, the energy of a neutral atom is given by [73, 76]

$$E^{\mathrm{at}} = \frac{3}{7} ZV_0 \ , \tag{18}$$

which is equivalent to

$$E^{\mathrm{at}} = \frac{3}{7} V_{\mathrm{ne}} \ . \tag{19}$$

However when the Thomas–Fermi values of V_0 are used in Eq. (18), the results are very poor, in error by as much as 30% [62,66]. Nevertheless, the form of Eq. (18) is suggestive, owing to its resemblance to the first term in the exact formula, Eq. (8). Equations (18) and (19) would follow from Eq. (8) if the integral term in the latter were equal to one-seventh of the first term, or invoking the virial theorem, if

$$V_{ne} = -7V_{ee} \quad . \tag{20}$$

It had already been demonstrated by Fraga [59] that this condition is roughly satisfied at the Hartree–Fock level; he then introduced it to obtain Eqs. (18) and (19) from the Hellmann–Feynman theorem and showed that using Hartree–Fock V_0 reduces the errors to about 2% [59, 62].

However Eq. (20) is rather an oversimplification. The ratio $|V_{ne}/V_{ee}|$ actually decreases rapidly across the first row, reaching a minimum of less than 6.0 for neon and then leveling off, after aluminum, at about 6.2–6.3 [68, 77, 78]. For most atoms, therefore, a factor in the neighborhood of 0.420 would be more appropriate in Eqs. (18) and (19) than the original three-sevenths (0.4286).

The relative success achieved for atoms by an expression as uncomplicated as Eq. (18) stimulated interest in finding a molecular equivalent. Since the rigorous formula for molecules, Eq. (9), is simply a summation over atomic terms, it seemed reasonable to test the same approach at the approximate level, i.e. [79]

$$E^{mol} = \frac{3}{7}\sum_{A} Z_A V_{0,A} \quad . \tag{21}$$

Equation (21) was found to reproduce Hartree–Fock and Kohn–Sham density functional total energies (exact were usually not available) to within about 1% [77, 79, 80, 81].

By combining Eqs. (13) and (21), the latter can be written as

$$E^{mol} = \frac{3}{7}(V_{ne} + 2V_{nn}) \quad , \tag{22}$$

which is the molecular analogue of Eq. (19). It is significant, however, that the simple summation relationship between the atomic and molecular expressions, whether rigorous or approximate, exists only when they are written in terms of electrostatic potentials at nuclei.

Just as in the atomic case, the approximate molecular formula, Eq. (21), would follow from the rigorous one, Eq. (9), if the integral term in the latter were one-seventh of the first term, or putting it alternatively, if

$$V_{ne} + 2V_{nn} = -7(V_{ee} - V_{nn}) \quad . \tag{23}$$

We have investigated the degree to which Eq. (23) is satisfied for 24 molecules, primarily diatomic and triatomic, at the density functional B3PW91/6-311+G(3df,2pd) level (Becke three-parameter hybrid functional [82] with Perdew–Wang 91 correlation [83]). The ratio $|(V_{ne} + 2V_{nn})/(V_{ee} - V_{nn})|$ averaged 6.65 with a root-mean-square deviation of 0.41 [84].

The relative success of Eq. (21) stimulated a great deal of interest which led to the development of a number of approximate energy relationships based upon electrostatic potentials at nuclei. Some of these are modifications of Eq. (21), while others reflect different approaches. As anticipated (Sect. 3.1), Hartree–Fock V_0 and $V_{0,A}$ were found to often produce energy quantities that are better than Hartree–Fock, sometimes nearly exact. This work has been reviewed by Levy et al. [66] and by Politzer [85, 86, 87]. The most recent versions of Eq. (21), which have the form

$$E^{mol} = \sum_{A} k_A Z_A V_{0,A} \quad , \tag{24}$$

where k_A is a parameter that depends upon the atom, achieve an accuracy of 0.10% relative to the estimated exact energies [68, 84]. Unfortunately the average error in hartrees is 0.123 (77 kcal/mol); thus, Eq. (24) cannot presently be used to calculate reaction energetics, however a variety of other applications have been found [68, 84].

4 Electronegativity

Parr et al. [52] have identified electronegativity with the negative of the chemical potential; for atoms

$$\chi^{at} = -\mu^{at} = -\left(\frac{\partial E^{at}}{\partial N}\right)_Z \tag{25}$$

and for molecules

$$\chi^{mol} = -\mu^{mol} = -\left(\frac{\partial E^{mol}}{\partial N}\right)_{v(\mathbf{r})} \quad . \tag{26}$$

They also showed that χ^{at} can be expressed rigorously (through μ^{at}) in terms of the electrostatic potential at the atom's nucleus [52]:

$$\chi^{at} = -\mu^{at} = V_0 - \left(\frac{\partial E^{at}}{\partial Z}\right)_{N=Z} \quad . \tag{27}$$

This was recently extended to neutral molecules [18]:

$$\chi^{mol} = -\mu^{mol} = V_{0,A} - \left(\frac{\partial E^{mol}}{\partial Z_A}\right)_{N=\sum_A Z_A} \quad . \tag{28}$$

Equations (27) and (28) represent, in principle, an unambiguous means for determining electronegativities. Unfortunately they are given as small differences between large quantities; thus, any error in the latter is greatly magnified in χ^{at} and χ^{mol}.

Another route to the electronegativity, also involving the electrostatic potential, is provided by a fundamental relationship of density functional theory [2, 52, 73]:

$$\mu = \frac{\delta \mathbf{T}[\rho]}{\delta\rho} - V(\mathbf{r}) + \frac{\delta\varepsilon_x[\rho]}{\delta\rho} + \frac{\delta\varepsilon_c[\rho]}{\delta\rho} \quad . \tag{29}$$

$\mathbf{T}$, ε_x and ε_c are the kinetic, exchange and correlation energy functionals, respectively. It should be noted that μ is a constant for a given system [2, 52, 88], even though all the quantities on the right side of Eq. (29) are functions of $\mathbf{r}$. If the functional derivatives in Eq. (29) can be evaluated for an atom or molecule, or if a point $\mathbf{r}$ can be found where their sum is zero, then knowledge of $V(\mathbf{r})$ will permit the determination of μ^{at} or μ^{mol} (and hence χ^{at} or χ^{mol}). Efforts to locate such points have been made [89, 90, 91], and Deb et al. [91] found their estimated magnitudes for atoms and monatomic ions to correlate with various properties, within families in the periodic table. However, Eq. (29) has not, so far, provided a successful approach to the determination of electronegativities.

5 Noncovalent interactions

As discussed in Sect. 2.1, molecules typically have some regions of negative electrostatic potential, in which are necessarily found one or more local minima, V_{min}, i.e. points at which $V(\mathbf{r})$ achieves its most negative values. It might seem reasonable to regard these as the sites most likely to undergo electrophilic attack, and this interpretation has indeed met with some degree of success [22, 23, 24, 25, 26]. The V_{min} are, however, not consistently reliable for this purpose. One reason for this is that $V(\mathbf{r})$ is normally computed for the unperturbed ground state molecule, and thus does not reflect any polarization effects produced by the approaching electrophile [24, 92]. (A number of studies have attempted to correct for this, for example, by means of perturbation theory; see the early review by Politzer and Daiker [24] as well as later work [93, 94, 95].) Another factor is that the most negative regions may not be the locales of the most reactive electrons [96, 97, 98, 99]. These problems can be minimized by focusing upon noncovalent interactions, which are primarily electrostatic in nature [56, 100, 101, 102, 103], but in which the separations are sufficient that polarization and charge transfer are not significant. This includes the early stages of biological "recognition" processes, for example, between drugs and receptors or enzymes and substrates, and the application of electrostatic potentials to their analysis has a long history [24, 25, 103, 104, 105, 106, 107].

In dealing with noncovalent interactions, it seems reasonable to look at the electrostatic potentials on the three-dimensional "surfaces" of the molecules, since it is through these that they "see" or "feel" each other. There is of course no rigorous basis for defining a molecular surface. A common approach has been in terms of a set of fused spheres centered on the individual nuclei and having some appropriate radii, for example, van der Waals [108, 109, 110, 111]. We prefer to follow Bader et al. [112] and use an outer contour of the electronic density, normally $\rho(\mathbf{r}) = 0.001$ e/bohr^3. This has the advantage that it reflects the specific features of the molecule, such as lone pairs, strained bonds, etc. Other contours of low magnitudes of $\rho(\mathbf{r})$, e.g. 0.002 e/bohr^3, would serve equally well [113]. For an excellent discussion and overview of treating electrostatic interactions, focusing upon biological systems, see Ref. [114].)

Considerable insight can sometimes be obtained from the qualitative examination of the electrostatic potentials on molecular surfaces [107, 115] (or in earlier years, in planes above the molecules [24, 25, 104, 106]). For example, this can reveal patterns of positive and negative regions that promote or inhibit certain interactions. Over a period of time, however, we have also developed a quantitative approach, which is based upon a detailed characterization of the molecular surface electrostatic potential, $V_{\mathrm{S}}(\mathbf{r})$, in terms of certain statistically defined quantities. Two of these are site-specific: the most negative and most positive values of $V_{\mathrm{S}}(\mathbf{r})$, designated $V_{\mathrm{S,min}}$ and $V_{\mathrm{S,max}}$. While Pathak and Gadre [27] proved that the only maxima of $V(\mathbf{r})$ in three-dimensional space are those associated with the nuclei, as mentioned in Sect. 2.1, this does not preclude maxima in the potential on the surface, $V_{\mathrm{S}}(\mathbf{r})$. The other quantities that we use to characterize $V_{\mathrm{S}}(\mathbf{r})$ are global in nature; they include

1. The average positive and negative potentials over the entire surface, $\bar{V}_{\mathrm{S}}^{+}$ and $\bar{V}_{\mathrm{S}}^{-}$

$$\bar{V}_{\mathrm{S}}^{+} = \frac{1}{\alpha}\sum_{j=1}^{\alpha} V_{\mathrm{S}}^{+}(\mathbf{r}_j) \ , \tag{30}$$

$$\bar{V}_{\mathrm{S}}^{-} = \frac{1}{\beta}\sum_{k=1}^{\beta} V_{\mathrm{S}}^{-}(\mathbf{r}_k) \ . \tag{31}$$

2. The average deviation, Π,

$$\Pi = \frac{1}{n}\sum_{i=1}^{n} |V_{\mathrm{S}}(\mathbf{r}_i) - \bar{V}_{\mathrm{S}}| \ . \tag{32}$$

3. The positive, negative and total variances, σ_{+}^{2}, σ_{-}^{2} and $\sigma_{\mathrm{tot}}^{2}$,

$$\begin{aligned}\sigma_{\mathrm{tot}}^{2} &= \sigma_{+}^{2} + \sigma_{-}^{2} \\ &= \frac{1}{\alpha}\sum_{j=1}^{\alpha}\left[V_{\mathrm{S}}^{+}(\mathbf{r}_j) - \bar{V}_{\mathrm{S}}^{+}\right]^2 + \frac{1}{\beta}\sum_{k=1}^{\beta}\left[V_{\mathrm{S}}^{-}(\mathbf{r}_k) - \bar{V}_{\mathrm{S}}^{-}\right]^2 \ .\end{aligned} \tag{33}$$

4. A balance parameter, v,

$$v = \frac{\sigma_{+}^{2}\sigma_{-}^{2}}{\left(\sigma_{\mathrm{tot}}^{2}\right)^2} \ . \tag{34}$$

In Eq. (32), $\bar{V}_{\mathrm{S}}$ is the overall average of $V_{\mathrm{S}}(\mathbf{r})$,

$$\bar{V}_{\mathrm{S}} = \left(\alpha\bar{V}_{\mathrm{S}}^{+} + \beta\bar{V}_{\mathrm{S}}^{-}\right)/(\alpha + \beta) \ . \tag{35}$$

Π was introduced as a measure of internal charge separation, which can be substantial even in molecules with zero dipole moment, such as *p*-dinitrobenzene; it correlates with several empirical indices of polarity [116, 117]. The variances σ_{+}^{2}, σ_{-}^{2} and $\sigma_{\mathrm{tot}}^{2}$ reflect the range, or variability, of the positive, negative and overall surface potentials, i.e. $V_{\mathrm{S}}^{+}(\mathbf{r})$, $V_{\mathrm{S}}^{-}(\mathbf{r})$ and $V_{\mathrm{S}}(\mathbf{r})$ [118, 119]. Since the terms in Eq. (33) are squared, the variances are very sensitive to the extremes of $V_{\mathrm{S}}(\mathbf{r})$; thus, $\sigma_{\mathrm{tot}}^{2}$ is generally much larger than Π and does not necessarily even show the same trend in a series of molecules [117]. Finally, the role of v is to indicate the level of balance between the strengths of the positive and negative surface potentials [118, 119]. When $\sigma_{+}^{2} = \sigma_{-}^{2}$, v has its maximum possible value, 0.250. The closer that v is to 0.250, the better the molecule can interact through both its positive and negative regions, whether this be strongly or weakly.

We have now evaluated the quantities defined in Eqs. (30), (31), (32), (33) and (34), plus $V_{\mathrm{S,max}}$, $V_{\mathrm{S,min}}$ and the positive and negative surface areas, A_{S}^{+} and A_{S}^{-}, for roughly 300 molecules, primarily organic. Some of these data are available in various locations [117, 120, 121, 122, 123, 124, 125]. We find most molecules have positive potentials on 60–75% of their surfaces, i.e. $A_S^+ > A_S^-$, but the negative potentials are usually stronger; thus, $|\bar{V}_S^-| > \bar{V}_S^+$ and $\sigma_-^2 > \sigma_+^2$. The imbalance between σ_-^2 and σ_+^2 is often quite severe, sometimes even an order of magnitude. However when there are several strongly electron attracting substituents competing for the polarizable electronic charge, so that each receives less of it, $|\bar{V}_S^-|$ and σ_-^2 decrease, and it can happen that $\bar{V}_S^+ > |\bar{V}_S^-|$ and $\sigma_+^2 > \sigma_-^2$. Two examples are CF_2Cl_2 and 1,3,5-trinitrobenzene [124]. Indeed this atypical situation is quite common among nitro-substituted energetic compounds (e.g. explosives and propellants), and we have been able to relate it quantitatively to their impact sensitivities [123].

The global and site-specific quantities that have been enumerated permit a thorough characterization of the electrostatic potential on a molecular surface. The significance of this is that we have succeeded, using small subsets of these quantities, in developing analytical representations of a variety of liquid-, solid- and solution-phase macroscopic properties that depend upon noncovalent interactions. These include heats of vaporization, sublimation and fusion, boiling points and critical constants, partition coefficients, solubilities and solvation energies, surface tensions, viscosities, diffusion constants, and liquid and crystal densities. This work has been reviewed elsewhere [117, 121, 124, 126, 127]. Recently it has been extended to include interactions in biological systems [107, 115, 125], for example, the potencies of reverse transcriptase inhibitors as anti-HIV agents.

Our approach can be summarized conceptually in terms of a general interaction properties function (GIPF),

$$\text{Property} = f\left(V_{S,\min}, V_{S,\max}, \bar{V}_S^+, \bar{V}_S^-, \Pi, \sigma_+^2, \sigma_-^2, \sigma_{\text{tot}}^2, \nu, A_S^+, A_S^-\right), \tag{36}$$

but noting that our expressions normally involve, in various combinations, only three or four of the quantities on the right side of Eq. (36). We require an experimental database consisting of the property of interest for as many compounds as possible; the variables in Eq. (36) are then computed for the corresponding molecules and a statistical analysis package is utilized to determine which subset of these variables provides the best fit of the database.

As examples, Eqs. (37) and (38) show our GIPF representations of heats of sublimation [128] and free energies of solvation in 1-octanol [129]:

$$\Delta H_{\text{subl}} = \alpha_1 A_S^2 + \beta_1\left(\nu\sigma_{\text{tot}}^2\right)^{0.5} - \gamma_1 \ , \tag{37}$$

$$\Delta G_{\text{solv}} = -\alpha_2 A_S^{0.5} - \beta_2\left(V_{S,\max}\right)^3 + \gamma_2 V_{S,\min} + \delta_2\left(\sigma_-^2\right)^2 + \varepsilon_2 \ . \tag{38}$$

In these equations, A_S is the total surface area, $A_S = A_S^+ + A_S^-$; the coefficients $\alpha_i, \beta_i, \gamma_i$, etc., are all positive. The correlation coefficients for Eqs. (37) and (38) are 0.950 and 0.984, respectively.

We make the relationships as general as possible, even though the correlations could undoubtedly be improved by treating different chemical classes separately, and we use as few of the computed quantities as is consistent with good accuracy, in order to gain insight into the key physical factors involved in the interactions. An important feature of the GIPF procedure is that liquid-, solid- and solution-phase properties are expressed in terms of quantities computed for individual molecules; the surroundings are not explicitly taken into account. Finally, since the entire procedure is computational (once the GIPF representation of a given property has been established), it can be applied to predicting properties for compounds that may not even have been synthesized, and thus it can be utilized in molecular design [130, 131].

6 Summary

We have focused successively upon several different aspects of the electrostatic potential: its distribution in three-dimensional space, $V(\mathbf{r})$; its minima along the internuclear axes between bonded atoms, defined by the condition $\nabla V(\mathbf{r}_m)\cdot\mathbf{u} = 0$; its values at the nuclei of atoms and molecules, V_0 and $V_{0,A}$; and its variation on molecular surfaces, $V_S(\mathbf{r})$. The common theme has been to show the variety of atomic and molecular properties that can be related to the electrostatic potential, whether rigorously or approximately. These range from intrinsic features (such as energies, covalent and anionic radii and electronegativities) to a wide array of properties that depend upon noncovalent interactions. Our objective has been to demonstrate that the electrostatic potential can be regarded as a fundamental factor in determining the natures and behavior of atoms and molecules.

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