Pergamon

QUANTUM CHEMICAL DESCRIPTORS FOR LINEAR SOLVATION ENERGY RELATIONSHIPS*

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Abstract—Linear solvation energy relationships (LSER) have been successfully used to correlate over 300 complex chemical and biochemical properties with small sets of descriptors related to fundamental characteristics of molecular structure and chemistry. This is a branch of the *unnamed science* (after Hansch) which is concerned with the intricate interactions between chemicals and life. Until recently, the descriptors in these relationships have been empirically determined. Recent developments in both the experimental understanding of these descriptors and in molecular orbital calculations have provided a new ground for fertile interaction between computational and experimental techniques. This manuscript describes development in the use of LSER and the recent molecular orbital formulations which provide basic descriptors developed from fundamental computational techniques. Examples from current research are presented to illustrate the expanding areas of chemistry accessible to these new ideas.

INTRODUCTION

The interaction of organic compounds with life or components of living organisms has been studied in a myriad of ways in fields of science ranging from abstract mathematics, computational science, chemistry, biology, environmental science, physics and even astronomical observations of organic molecules in the reaches of intergalactic space. The focus of these studies on life entails an inherent complexity which is characteristic of this work. The unifying theme of the life focus has prompted Hansch to designate these studies as a new field of as yet *unnamed science* (Hansch, 1993). This lack of a consistent designation does not appear to inhibit an estimated world wide economic investment of $40 billion a year in this field (Hansch, 1993).

One of the successful ideas in this field of science is that there are systematic relationships between related molecules that may be described in a quantitative manner based on a few common aspects of molecular structure (Hansch & Leo, 1979). The connections between structure and reactivity were reviewed early on by Burkhardt (1935) and Hammett

(1935). The pioneering work of Hammett established the usefulness of a parametric procedure, associated with molecular electronic structure, for understanding reaction rate constants or equilibrium constants (Hammett & Pfluger, 1933). In particular, the Hammet equation correlates acidity of substituted benzoic acids with a parameter σ associated with substitution on the aromatic ring (Hammett, 1937). Later work of Taft examined aliphatic esters and extended the Hammett equation to include a parameter E_S which correlated with steric effects of substituants near the reaction center (Taft, 1956). The work of Hansch broadened the ideas of the Hammett equation to include biological activities by incorporating an additional aspect of molecular structure related to the concept of hydrophobicity (Hansch, 1969). The increased complexity of biological activities encompasses such problems as transport and metabolic transformation of the organic compounds under consideration; the Hansch extension of the Hammett equations is described as the extra-thermodynamic approach in recognition that the activity is not solely a function of the thermodynamic chemical potential (Franke, 1984). These ideas have lead to the development of the highly successful method of quantitative structure–activity relationships (QSAR) which is based on the hypothesis that microscopic structural features of a chemical compound may be related in a quantitative manner to macroscopic

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properties (Shorter, 1982). The QSAR methodology has been widely reviewed (Bersuker & Dimoglo, 1991; Hall & Kier, 1991; Silipo & Vittoria, 1991; Hansch, 1993) and is sufficiently popular to support a journal: *Quantitative Structure–Activity Relationships*.

In principle this unnamed science is the reductionist search for models that described complex chemical-life interactions in terms of a few simple variables that, particularly with current abilities in computational science, can hopefully be described in quantitative terms and usefully applied in predictive manners. This is a continuation of ideas that go back at least as far as the ancient alchemical elements of earth, air, fire and water (Cramer et al., 1993). Besides the extra-thermodynamic approach described above, there are many other methods for quantitative reduction of these complex problems into simpler and hypothetically more elementary phenomena (Lewis, 1992); among the more popular are methods based on pattern recognition (Free & Wilson, 1964; Fujita & Ban, 1971) and the mathematical techniques of principal component analysis (Martin et al., 1974; Chastrette et al., 1985). A subset of the more general class of chemical-life interaction are the problems involved in understanding the effects of solvation (Cramer et al., 1993).

LINEAR SOLVATION ENERGY RELATIONSHIPS

It is well understood that solubility is one of the essential components of chemical and biological activity. The method of linear solvation energy relationship (LSER) developed by Kamlet and Taft (1983) correlates solvent effects with various free energy properties. The approach has been generalized to explain biological activities in terms of specific solute descriptors associated with solvation (Kamlet et al., 1987; Cramer et al., 1993).

SOLVATION EFFECTS FOR ORGANIC COMPOUNDS

The interaction of molecules with solvents is clearly capable of producing dramatic effects on structure, reactivity, biological activity, equilibrium and reaction rate constants and a host of other aspects which are of central interest to chemistry (Reichart, 1990). Solvation models are of great interest in the fundamental understanding of such processes as enzyme substrate interactions where desolvation of the substrate may be a significant factor influencing the equilibrium constant for complex formation and the corresponding rate of enzymatic catalysis (Bash et al., 1987; Cramer & Truhlar, 1995). The ability to calculate free energy changes associated with solvation allows calculation of differential free energies in solution without having to model complex changes in hydrogen bonded networks, or conformational changes, or other differential solvation issues for

which there is little direct information (Cramer et al., 1993; Honig et al., 1993).

There has been a lot of work in modeling these complex processes using some set of fundamental molecular properties. Kamlet and Taft and coworkers established the highly successful *solvatochromic* method to explain solvent effects on various free energy properties (Abboud et al., 1977). The term *solvatochromic* is derived from the origin of this method in terms of explaining the effect solvent has on the color of an indicator which is used for quantitative determination of a set of fundamental molecular attributes, the *solvatochromic* parameters. Solvents were described by their ability to *accept* (β) and to *donate* (α) hydrogen bonds and by their dipolarity/polarizability (π^*). These parameters found use in the linear equation:

$$\log(\gamma) = c_0 + c_1 \cdot \alpha + c_2 \cdot \beta + c_3 \cdot \pi^*,$$

π^* = measure of a solvent's ability to stabilize a charge or a dipole,

α = measure of a solvent's ability to donate a hydrogen bond,

β = measure of a solvent's ability to accept a hydrogen bond.

It is important to recognize that the use of π^* was successful in the solvatochromic comparison method despite concerns about the physical meaning of a parameter related to "solvent polarity", a term subject to considerable controversy (Shorter, 1982).

Kamlet and coworkers (Kamlet et al., 1987) have given a generalized formulation of LSER:

Property = bulk/cavity term + dipolarizability

term + hydrogen bonding term(s) + intercept.

This formulation of the LSER relationships attempts to correlate microscopic (energetic, bonding) and macroscopic (thermodynamic) terms. The cavity (bulk) term is a measure of the energy needed to overcome cohesive solvent–solvent molecule interactions to form a cavity for the solute molecule (endoergic). The dipolarity/polarizability terms are measures of the energies of solute–solvent dipole and induced dipole interactions (exoergic) which contribute to solution formation. Hydrogen bonding terms measure the energy of interaction (exoergic) when a solute–solvent complex is formed. Respectively hydrogen bond acceptor basicity (HBAB) and hydrogen bond donor acidity (HBDA) refer to accepting/donating a proton from/to a neighboring molecule in keeping with Brønsted–Lowry acid–base definitions. Usually not all the terms in this equation are statistically significant for a particular property.

It was apparent to a group of chemists lead by Abraham, Doherty, Kamlet and Taft that this approach could be generalized to understand specific properties of solutes which could be used in LFER to correlate physiochemical properties in the QSAR model (Kamlet et al., 1984; Abraham & Whiting,

1991). A concerted research program has lead to the development of the following expressions for relating a physicochemical property *SP* to solvation descriptors characteristic of the solute molecules:

$$\log SP = c + r \cdot R_2 + s \cdot \pi^{H_2}$$
$$+ a \cdot \Sigma\alpha^{H_2} + b \cdot \Sigma\beta^{H_2} + v \cdot V_x$$

for processes in condensed phases and

$$\log SP = c + r \cdot R_2 + s \cdot \pi^{H_2}$$
$$+ a \cdot \Sigma\alpha^{H_2} + b \cdot \Sigma\beta^{H_2} + l \cdot \log L^{16}$$

for processes involving gas-condensed phase transfer

The meaning of the specific regression variables, as defined by Abraham, is given below (Abraham, 1993):

SP is a physicochemical parameter such as the octanol–water partition coefficient or a biological parameter such as an RD_{50} or LD_{50}.

R_2 is an adjusted molar refractivity (MR) index defined as (MR − MR for an alkane of the same molecular volume).

π^{H_2} is a Gibbs-energy related parameter back calculated from GLPC results and is equivalent to a gas–liquid partition coefficient.

$\Sigma\alpha^{H_2}$ is a hydrogen-bond acidity parameter derived from 1:1 hydrogen-bond complexes in tetrachloromethane solvent.

$\Sigma\beta^{H_2}$ is a hydrogen-bond basicity parameter derived from 1:1 hydrogen-bond complexes in tetrachloromethane solvent.

V_x is a molecular volume parameter that can be calculated from structural information and is used for condensed phase phenomena while $\log L^{16}$ is the solute–hexadecane partition coefficient for gas–liquid phenomena.

This scheme is similar in form to classical QSAR but now the regression variables are chemically derived as opposed to structurally derived (Cramer *et al.*, 1993).

Thermodynamic interpretation can be inferred from the work by Abraham and co-workers (Abraham *et al.*, 1990) on solute transfer from water to hexadecane. The volume (bulk) term is related to the difference in energy needed to create a solute molecule sized cavity in the two solvents; it is endoergic in each solvent. If this energy is greater in water, it will make the standard enthalpy change from water to hexadecane exothermic. The cavity term also seems to involve general dispersive forces; these will be more exoergic and exothermic in a nonpolar solvent than in water, again contributing to a more exothermic overall change. The dipolarity and polarizability terms are not as easily interpreted thermodynamically; however greater dipolarity implies a greater tendency to form solute–water dipole–dipole interactions which are expected to be exoergic. The hydrogen bonding terms involve the difference be-

tween the exothermic solute–water interaction and the much less exothermic solute–hexadecane interaction resulting in an overall endothermic enthalpy of transfer. However the entropy change from solute–water bonds will be less than that for solute–hexadecane bonds resulting in overall positive entropy change (Famini *et al.*, 1993).

REGRESSION VARIABLES BASED ON COMPUTATIONALLY DETERMINED QUANTITIES

The success of the solvatochromic comparison method of Kamlet and Taft, the QSAR methods associated with Hansch analysis and the new scales for solvation parameters defined by Abraham and coworkers has suggested that a small number of regression parameters might be associated with fundamental molecular quantities calculable by molecular orbital methods or other techniques of quantum chemistry (Lewis, 1990 & 1992). Ford and Livingstone (1990) have pointed out the advantages of computational derived descriptors. Among the most important are the fact that such descriptors are not restricted to related series of molecules and provide clearly defined properties associated with molecular structure and composition. Using semiempirical methods, Lewis calculated dipole moments, energies ΔE of HOMO–LUMO gaps at optimized molecular geometries, and other electronic properties (Lewis 1987 & 1990). There is significant correlation between these quantities and the polarity/polarizability parameter π^* and hydrogen bond basicity parameter β of Kamlet and Taft (Lewis, 1987). Using the semiempirical MINDO/3 method, dipole moments were calculated for 50 compounds. Neglecting acetic acid as an outlying point due to possible dimerization, the regression equation for the remaining calculated values correlated with the experimental values with an R factor of 0.827. The ratio of the electrophilic superdelocalizability and the HOMO–LUMO gap, ΔE, was found to correlate with 32 experimental values for molecular polarizability with an R factor of 0.946. For 14 compounds, π^* was found to correlate with calculated dipole moments with an R factor of 0.916 and β was found to correlate with the ratio of the calculated dipole moment over ΔE with an R factor of 0.813.

THEORETICAL LINEAR SOLVATION ENERGY RELATIONSHIPS

Famini and coworkers have investigated the parameters in the generalized LSER equations using computational techniques (Famini 1988a, b; Famini *et al.*, 1991, 1993, 1992; Famini & Wilson, 1992, 1994). They have developed the Theoretical Linear Solvation Energy Relationship (TLSER) method based on a systematic study of this problem. The TLSER formulation of the regression equations is given by:

$$\log P = m \cdot V_{mc} + p \cdot \pi_1 + a \cdot \epsilon_a$$
$$+ a' \cdot Q_H + b \cdot \epsilon_b + b' \cdot Q_- + \text{intercept}.$$

The TLSER regression variables have the following definitions:

log P is the logarithm of the experimental property. V_{mc} is the steric term given by the calculated Van der Waals volume, in this case using a method given by Hopfinger.

π_1 is the molecular polarizability calculated in the MOPAC package divided by V_{mc} to give a volume independent term.

The hydrogen bonding terms are divided into acid (acceptor) and base (donor) terms. They are further separated into covalent and electrostatic terms that reflect the different aspects of bonding, particularly intermolecular interactions which may exhibit differing characteristics:

ϵ_a is the energy of the lowest unoccupied molecular orbital, LUMO, relative the HOMO for water calculated using the same semiempirical formulation. This reflects the covalent part of the acidity or acceptor term.

Q_{H+} is the atomic formal charge on the most positive hydrogen atom in the calculation. This reflects the electrostatic part of the acidity or acceptor term.

ϵ_b is the energy of the highest occupied molecular orbital HOMO, relative to the LUMO for water. This reflects the covalent part of the basicity or donor term.

q_- is the atomic formal charge on the most negative nonhydrogen atom in the calculation. This reflects the electrostatic part of the donor or basicity term.

The molecules of interest for these studies are large. Therefore, the TLSER method relies on the semiempirical formulations for molecular orbital calculations (Stewart, 1990b; Zerner, 1991), most notably the well-documented and extensive functionalities available in the MOPAC package (Stewart, 1990a). These descriptors have been successfully used to understand a range of properties including charcoal absorption, HPLC retention index, electronic absorption of pyridinium ylides in different solvents, octanol–water partition coefficients, *pKa*, and rate constants for hydrolysis of organophosphonothioates (Famini *et al.*, 1992a; Cramer *et al.*, 1993).

REGRESSION VARIABLES DETERMINED FROM *AB INITIO* CALCULATIONS

Politzer and coworkers have done considerable work on using electrostatic potentials computed on molecular surfaces, from *ab initio* wave functions, to interpret the solvatochromic parameters (Politzer

et al., 1993). The electrostatic potential $V(r)$ is defined as:

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')\,dr'}{|r' - r|},$$

where Z_A is the charge on nucleus A, located at R_A and $\rho(r)$ is the electronic density of the molecule. Their early studies found good correlations between the Kamlet–Taft β, which is a solvent's ability to accept a proton (basicity), and the most negative values of the molecular electrostatic potential associated with atoms in the solvent molecule accepting the proton (Murray *et al.*, 1991). Because the most positive regions of the electrostatic potential occur at the positions of the nuclei, there is no direct correlation between the maxima of $V(r)$ and affinities for nucleophilic processes similar to the relationship between negative regions and the affinity for electrophilic processes. However, variations of $V(r)$ on a surface are useful indicators. They found good correlations with the Kamlet–Taft α, a solvent's hydrogen bond donating parameter, and maxima of electrostatic potential functions calculated on a surface of 0.002 electron/bohr^3 electron density (Murray & Politzer, 1991). Further work has confirmed similar relationships between the solute hydrogen bond basicity and acidity scales of Abraham as discussed above (Murray & Politzer, 1992). They have proposed further use of the electrostatic potential by defining quantities related to the variance of the electrostatic potential on the molecular surface, as defined by Bader, of density 0.001 electron/bohr^3 (Murray *et al.*, 1993; Politzer *et al.*, 1993b). They define a total variance σ^2_{tot}:

$$\sigma^2_{tot} = \sigma^2_+ + \sigma^2_-,$$

where σ^2_+ and σ^2_- are variances of the surface electrostatic potential in positive and negative regions, respectively. For 21 organic compounds, they found that solubility in supercritical CO_2 varied inversely with the variance of the electrostatic potential consistent with solute–solute interactions dominating over solute–solvent interactions in low density supercritical solutions (Politzer *et al.*, 1993b). Finally, they introduce a quantity Π, described as local polarity, which represents the average deviation of the electrostatic potential over the molecular surface:

$$\Pi = \frac{1}{N} \sum_{i=1}^n |V_{S_i} \bar{V}_S|$$

where V_{S_i} represents the electrostatic potential calculated at point on the surface and $\bar{V}_S$ represents the average value of these points over the whole surface. For 70 molecules, they find that the octano–water partition coefficient can be represented in terms of the molecular surface area, the variance of the electrostatic potential σ^2_{tot} and the average deviation Π (Brinck *et al.*, 1993).

EXAMPLES FROM RECENT RESEARCH

Famini and co-workers have recently applied the TLSER method to study gas phase acidities of some carboxylic acids, alcohols, silanols, anilines, hydrocarbons and oximes (Famini *et al.*, 1993). Gas phase acidity is described as the enthalpy change required to remove a proton from a molecule:

$$AH \xrightarrow{\Delta H} A^- + H^+.$$
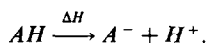
Quantitative data on gas phase acidity data may be determined experimentally through high-pressure mass spectrometry, ion cyclotron resonance and flowing afterglow methods and is given in terms of standard enthalpy change. It is important to note that increasing enthalpy change means decreasing acidity. The acidity for the hydrocarbon molecules was modeled by using the activation energy for MgO catalyzed hydrogen and deuterium exchange. The entropy changes associated with deprotonation of the molecules studied could be calculated from the partition function and are all near $100 \, J \, mol^{-1}$.

The TLSER regression fit for gas phase acidity on combined sets of these molecules yielded R factors of 0.970 or higher. Not all of the descriptors are statistically significant for each of the types of molecules. The volume terms are significant, with negative signs, for the acids and alcohols. This might be associated with an inductive effect which is expected to be larger for larger molecules. One or both of the hydrogen bond acidity descriptors are included in the correlations for combined sets; their signs are negative indicating that increasing acidity decreases the standard enthalpy change. The hydrogen basicity term Q_- is significant for alcohols, acids and silanols with a positive sign indicating that increased basicity increases ΔH_a as expected. The hydrogen basicity term ϵ_b occurs for the acids, alcohols, anilines and hydrocarbons. The sign is different for the hydrocarbons possibly as a resulting of modeling acidity with MgO catalysis. The dipolarity/polarizability term π_1 was less significant in the regression fits and there is no ready explanation for its associated signs in various correlations.

Famini and Wilson (1994) have studied the reaction rate for decarboxylation of substituted 3-carboxybenzisoxazoles, which occur in various solvents in the presence of the base tetramethyl guanidine. From a multiple correlation study of similar solute molecules in several solvents, they draw the following conclusions based on the TLSER descriptors; the reaction rate decreases with increasing solvent hydrogen bond donating acidity. This suggests that the solvent forms a complex witht the solute in which the charge is localized near the carboxy group hindering the loss of the neutral molecule. The reaction rate increases with increasing solvent accepting hydrogen bond basicity. This suggests that the solvent forms a complex with the tetramethylguanidinium ion freeing the solute ion and allowing the charge to delocalize thus facilitating the loss of the neutral carbon dioxide. The change in the descriptors over a set of substituted solute molecules is similarly associated with the ability of the charge to be distributed over the free solute ion enhancing the release of the neutral carbon dioxide molecule. There is not strong support for the reaction rate enhancement through dispersive interactions stabilizing a transition state. Also important was inclusion of an empirical Hildebrand solubility parameter (cohesive energy density) as a solvent cohesive parameter with the TLSER descriptors. The proposed alternative use of a reciprocal solvent volume parameter was not significant for these studies.

Cramer and coworkers (Cramer *et al.*, 1993) have investigated the TLSER formalism using computational techniques, based on continuum solvation models. This demonstrates effective differences from standard computational techniques which assume an isolated molecule in the gas phase. This is because standard calculations may be inadequate to understand biological properties measured *in vivo* or *in vitro* assays in aqueous environments. Thus in these cases, aqueous solvation appears to play a role in the observed inhibition of dopamine transporter uptake by cocaine analogs. TLSER descriptors calculated using AM1 gas phase models were unsuccessful in producing a statistically significant correlation for these analogs. However, the AM1-SM2 model Hamiltonian produced a significant correlation ($N = 13, R = 0.876, S = 0.675, F = 16.6$) with the calculated free energy of solvation and the charge on the most positively charged hydrogen.

Headly and coworkers (Headly *et al.*, 1995) have studied the acidity of 25 substituted acetic acids in seven different solvents using the TLSER methodology. They find that the acidity variations in water are dictated primarily by the acidic properties of water. In alcoholic solvents, the ability to form a cavity in the solvent and the solvation of the potential acidic proton are important contributions for acidity determination. For non-acidic solvents, such as dimethoxyethane, only the interaction of the potential acidic proton is important for acidity variations. Accurate prediction for the acidity of N,N-dimethylglycine was obtained for all seven solvents demonstrating the success of the TLSER descriptors in modeling the solute–solvent interactions that account for the tautomerization of amino acids.

Politzer and coworkers have extended their work into the formulation of a general interaction properties function (GIPF) based on an *ab initio* wavefunction. They propose a generalized equation for the prediction of macroscopic properties that includes calculated molecular terms that represent global quantities and site-specific quantities (Politzer & Murray, 1994). They propose descriptors of macroscopic properties based on molecular area, local

surface ionization energies and statistically based interaction indices derived from molecular surface electrostatic potentials. This GIPF has the following form:

$$\text{property} = f[\text{area}, \bar{I}_{S,min}, V_{S,max}, V_{S,min}, \Pi, \sigma_{tot}^2, \gamma]$$

The *site-specific* molecular quantities of this GIPF are described as follows:

$\bar{I}_{S,min}$ is the minimum molecular ionization potential found on the surface calculated at 0.001 au contour. This reflects the tendency for charge transfer at any particular molecular site.

$V_{S,max}$, $V_{S,min}$ are the maximum and minimum electrostatic potential on this surface. The maximum reflects the tendency for long-range attraction of nucleophiles at a specific site, the minimum reflects the tendency for long range attraction of electrophiles at a specific *site*.

The *global* molecular quantities of the GIPF are described as follows:

area represents the size of the molecule. This is a cavity term equivalent to the use of molecular volume in other approaches.

Π is the local polarity as defined previously.

σ_{tot}^2 represents the variability of the surface electrostatic potential, as defined previously.

γ is an electrostatic balance term and is defined in terms of the positive, negative and total variances:

$$\gamma = \frac{\sigma_+^2 \, \sigma_-^2}{[\sigma_{tot}^2]}$$

They have found correlations between electrostatic potential minima $V_{S,min}$ and solvent hydrogen bond accepting parameter β and the solute hydrogen bond accepting parameter β^{H_2} for four families of molecules containing hydrogen-bond-accepting heteroatoms, taken separately. For azines, alkyl ethers, primary amines and molecules containing double bonded oxygen such as DMSO, the electrostatic potential in the space around a gas phase molecule is a key (but not sole) factor determining its ability to accept a proton in solute–solvent hydrogen bonding. There are good correlations between the solvent hydrogen bond donating parameter, α, the solute hydrogen bond donating parameter α^{H_2}, and $V_{S,max}$ for molecules such as acetonitrile, butanone, nitromethane and phenols. For nitromethane, acetonitrile, acetone and butanone, the correlation coefficients for α, with $V_{S,max}$ was 0.98. For the same molecules plus six phenols, the correlation between $V_{S,max}$ and α^{H_2} was 0.98. They find that these parameters are best represented by more complex relationships between the GIPF descriptors:

$$\beta_2^H = f[\bar{I}_{S,min}, V_{S,min}, \Pi]$$

$$\alpha_2^H = f[\text{area}, \sigma_+^2 \, V_{S,max}, \gamma\sigma_{tot}^2].$$

CONCLUSIONS

The purpose of this article is to briefly review the emerging role of quantum chemistry in the *unnamed science*. We have briefly outlined the parameterization of the chemical-life interactions in terms of molecular solvation properties and examine the computational studies of these solvation properties in terms of fundamental quantum chemical phenomena. The intention is to illustrate how our understanding of molecular structure and function, based on first principles, may be related to understanding of the complex interactions that are characteristic of the unnamed science. It is clear that calculations based on various Hamiltonians have been useful in understanding a wide variety of biological phenomena suggesting that the reductionist search for basic molecular properties has significance beyond the scope of the orginal computations. Since the number of theoretical descriptors which can be retrieved from a single calculation is quite large, it is possible to experiment with a variety of chemical interpretations and rely on the regression analysis to eliminate those descriptors that are unimportant. The objective is to provide insight into the chemistry under study, especially by consideration of the sign and magnitude of the regression coefficient associated with particular properties (Cramer *et al.*, 1993). This article demonstrates that the tools and technology are available for novel studies of complex chemical-life interactions based on fundamental molecular properties determined by quantum chemical techniques.

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