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Correlations between the Solvent Hydrogen-Bond-Donating Parameter α and the Calculated Molecular Surface Electrostatic Potential

Jane S. Murray and Peter Politzer*

University of New Orleans, Department of Chemistry, New Orleans, Louisiana 70148

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Introduction

Linear solvation energy relationships based upon the use of "solvatochromic parameters" have resulted from an extensive effort to separate and identify certain solvent properties and to quantitatively determine their effects on various experimentally observed quantities (e.g., rate constants, equilibrium constants, and IR, NMR, ESR, and UV/vis absorption maxima and intensities).[1-5] These relationships have been used successfully to correlate a large number of solute/solvent and biological properties,[6,7] including some in supercritical solutions.[8-10] Two of the solvatochromic parameters, designated as α and β, have been interpreted as providing measures of a solvent's ability to *donate* or to *accept* a proton in solute–solvent hydrogen bonding.[5]

We have recently demonstrated that the calculated electrostatic potential minima in several families of hydrogen-bond-accepting solvents (primary amines, azines, alkyl ethers and molecules containing double-bonded oxygens), treated separately, correlate well with the corresponding hydrogen-bond-acceptor parameters β.[11] This confirms that the electrostatic potential created in the space around a gas-phase molecule is a key factor in determining its ability to *accept* a proton in a solute-to-solvent hydrogen bond and provides a practical means for predicting unknown β values. In this work, we have extended our analysis to explore the possibility of relationships between the calculated electrostatic potential and the hydrogen-bond-donating parameter α.

Methods and Procedure

The electrostatic potential $V(\mathbf{r})$ created in the space around a molecule by its nuclei and electrons is expressed rigorously by eq 1:

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

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$; $\rho(\mathbf{r})$ is the electronic density function of the molecule, which we obtain from an ab initio self-consistent-field molecular orbital (SCF-MO) wave function. $V(\mathbf{r})$ has emerged over the past two decades as an effective analytical tool in interpreting and predicting the reactive behavior of molecules.[12-16] An important feature of the electrostatic potential is that it is a real physical property, which can be determined both experimentally, by diffraction methods, as well as computationally.[13]

The first term on the right side of eq 1 represents the contribution of the nuclei, which is positive; the second term brings in the effect of the electrons, which is negative. The sign of $V(\mathbf{r})$ in any particular region depends, therefore, upon whether the effects of the nuclei or electrons are dominant there. An approaching electrophile (including a proton donor in a hydrogen bond) will initially be attracted to those regions in which $V(\mathbf{r})$ is negative, and in particular to the points where $V(\mathbf{r})$ has its most negative values, $V_{\min}$ (the local minima).

Table I. Hydrogen-Bond-Donating Parameters α^a and Calculated Surface Electrostatic Potential Maxima, $V_{S,\max}$, for Some Molecules Containing –OH Groups

molecule	hydrogen-bond-donating parameter[a] α	$V_{S,\max}$, (kcal/mol)
$F_3CCH(OH)CF_3$	1.96	49.6
F_3CCH_2OH	1.51	48.6
H_2O	1.17	38.0
CH_3COOH	1.12	39.0
CH_3OH	0.93	37.3
$HOCH_2CH_2OH$	0.90	37.1
CH_3CH_2OH	0.83	35.6
$CH_3CH_2CH_2CH_2OH$	0.79	34.6
$CH_3CH_2CH_2OH$	0.78	35.6
$CH_3CH(OH)CH_3$	0.76	35.0
$(CH_3)_3COH$	0.68	31.4

[a] The hydrogen-bond-donating parameters α are taken from ref 5.

Table II. Hydrogen-Bond-Donating Parameters α^a and Calculated Surface Electrostatic Potential Maxima, $V_{S,\max}$, for Some Molecules in which Alkyl Groups Are the Hydrogen Donors

molecule	hydrogen-bond-donating parameter[a] α	$V_{S,\max}$ (kcal/mol)
CH_3NO_2	0.22	32.9
CH_3CN	0.19	27.4
$CH_3C(O)CH_3$	0.08	17.3
$CH_3CH_2C(O)CH_3$	0.06	18.4

[a] The hydrogen-bond-donating parameters α are taken from ref 5.

While the $V_{\min}$ are generally indicative of sites favorable for electrophilic attack, local maxima in the positive regions are not normally indicative of sites reactive toward nucleophiles. It has been shown that $V(\mathbf{r})$ has maxima only at the positions of the nuclei.[17] These reflect the magnitudes of the nuclear charges and therefore cannot be assumed to indicate relative affinities for nucleophiles. Nevertheless, it has proven to be possible to use the electrostatic potential to interpret and predict nucleophilic processes, although by procedures that are less straightforward than for electrophilic ones.[18-24] A particularly useful approach

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* Author to whom correspondence should be addressed.

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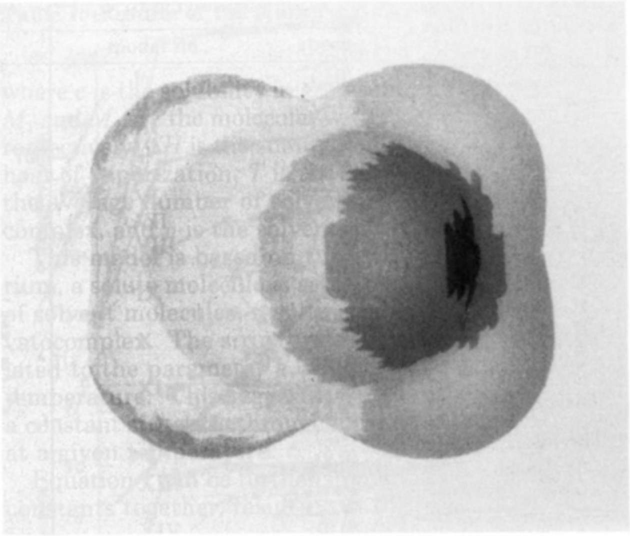

Figure 1. Calculated electrostatic potential on the molecular surface of ethanol. The hydroxyl group is facing the viewer. Four ranges of $V(\mathbf{r})$ are depicted, in kcal/mol. In order of increasingly dark shading, these ranges are: $V(\mathbf{r}) < 0$; $0 < V(\mathbf{r}) < 20$; $20 < V(\mathbf{r}) < 34$; $34 < V(\mathbf{r})$.

involves examining $V(\mathbf{r})$ on the three-dimensional ground-state molecular surface, appropriately defined.[22,24]

In earlier studies of hydrogen-bonding interactions, regions of negative electrostatic potential have been used successfully to identify hydrogen-bond-acceptor sites.[14,25] Quite recently, as has already been mentioned, we have demonstrated that the electrostatic potential minima associated with the nitrogens in primary amines and azines and the oxygens in alkyl ethers, and molecules containing double-bonded oxygens, taken separately, correlate well with the hydrogen-bond-acceptor parameter β.[11]

However, in exploring the possibility of a relationship between $V(\mathbf{r})$ and the hydrogen-bond-donating parameter α, we have focused on the regions of positive $V(\mathbf{r})$ on a three-dimensional surface encompassing the molecule. Using STO-3G-optimized structures computed using GAUSSIAN 88,[26] we have calculated $V(\mathbf{r})$ at the STO-5G level on surfaces defined by the 0.002 electron/bohr^3 contour of the STO-5G electronic density $\rho(\mathbf{r})$[27] for the fifteen molecules listed in Tables I and II. The STO-5G basis set has been found to be reliable for properties related to the electronic density, such as $V(\mathbf{r})$.[13-16] It has been shown, for a group of diatomic molecules and for methane, that the 0.002 electrons/bohr^3 contour gives physically meaningful molecular dimensions and encompasses at least 95% of the electronic charge.[28,29]

The molecules for which we have carried out computations were selected because of the availability of their α values.[5] The most positive values of $V(\mathbf{r})$ found on the surfaces in the vicinities of hydrogens that could be donated in hydrogen bonds have been tabulated in Tables I and II; these are designated as $V_{S,max}$.

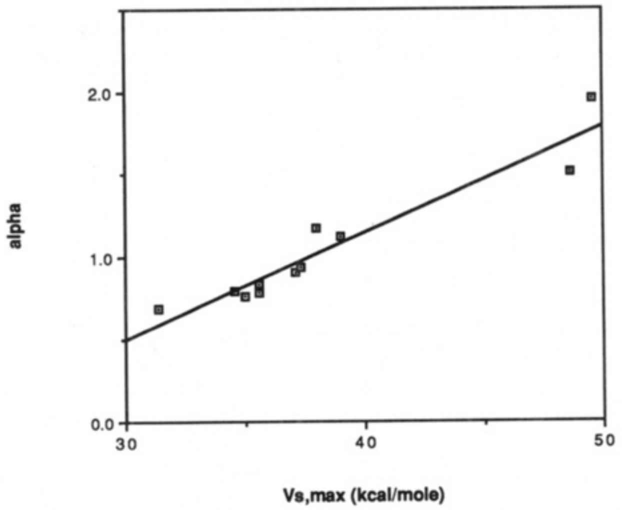

Figure 2. Correlation between $V_{S,max}$ and α for the group of molecules containing OH groups listed in Table I. The least-squares equation of the line is $\alpha = -1.466 + 0.0653V_{S,max}$, with a correlation coefficient of 0.96.

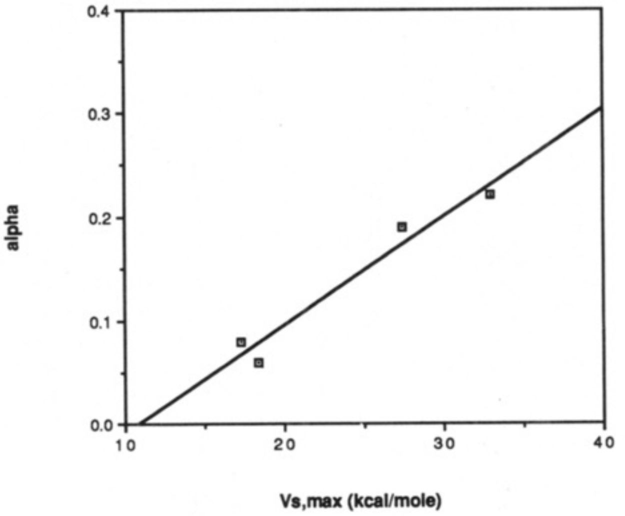

Figure 3. Correlation between $V_{S,max}$ and α for the molecules listed in Table II. The least-squares equation of the line is $\alpha = -0.111 + 0.0104V_{S,max}$, with a correlation coefficient of 0.98.

Results

Figure 1 shows the surface electrostatic potential of ethanol and illustrates our approach of obtaining the most positive value of $V(\mathbf{r})$ on a well-defined molecular surface. The $V_{S,max}$ of ethanol, 35.6 kcal/mol, is within the range of $V(\mathbf{r})$ shown in darkest shading and is associated with the hydroxyl hydrogen.

Our computed $V_{S,max}$ values for 11 molecules containing OH groups and for four others in which alkyl groups are the hydrogen donors are listed in Tables I and II, respectively. Within each group of molecules, the general tendency is for $V_{S,max}$ to decrease with diminishing α. Linear relationships between α and $V_{S,max}$ for the molecules in Tables I and II are presented in Figures 2 and 3; the correlation coefficients are 0.96 and 0.98, respectively.

Summary and Conclusion

We have demonstrated that good correlations exist between the solvatochromic hydrogen-bond-donating parameter α and $V_{S,max}$. Our results confirm that the cal-

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culated electrostatic potential of a gas-phase molecule can be quantitatively related to its ability in solution to *donate* a proton in a solvent-to-solute hydrogen bond, and thus provide a predictive capability for determining unknown α values. The fact that the two groups of molecules must be treated separately is indicative of roles played by other factors.

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Registry No. $F_3CCH(OH)CF_3$, 920-66-1; F_3CCH_2OH, 75-89-8; H_2O, 7732-18-5; CH_3COOH, 64-19-7; CH_3OH, 67-56-1; $HOCH_2CH_2OH$, 107-21-1; CH_3CH_2OH, 64-17-5; $CH_3CH_2CH_2CH_2OH$, 71-36-3; $CH_3CH_2CH_2OH$, 71-23-8; $CH_2CH(OH)XH_3$, 67-63-0; $(CH_3)_3COH$, 75-65-0; CH_3NO_2, 75-52-5; $CH_3C(O)CH_3$, 67-64-1; CH_3CN, 75-05-8; $CH_3CH_2C(O)CH_3$, 78-93-3.

Cyclopenta[*cd*]pyrene and Monomethyl Isomers

R. Sangaiah* and A. Gold

Department of Environmental Sciences and Engineering,
University of North Carolina at Chapel Hill, Chapel Hill,
North Carolina 27599-7400

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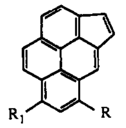
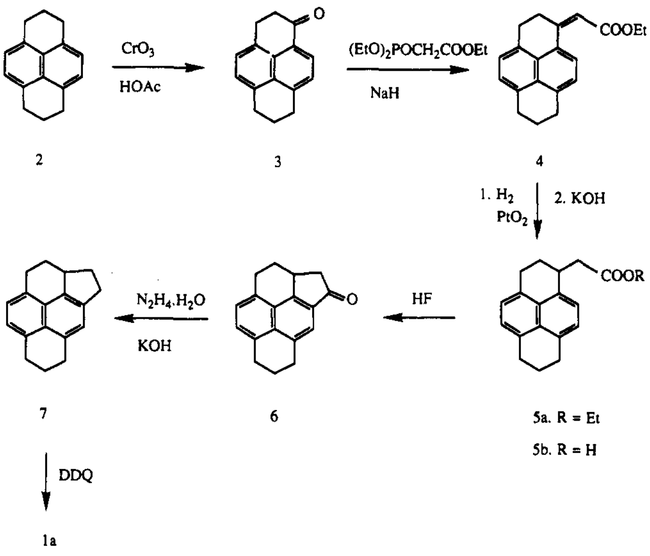
Introduction

Polycyclic aromatic hydrocarbons (PAH) and their methyl congeners are important environmental contaminants.[1] Cyclopenta[*cd*]pyrene (CPP) is an active mutagen[2] and carcinogen,[3] identified as a major extractable component of particulates from gasoline, kerosine, and coal combustion,[4-6] and its co-occurrence with methylated isomers is suggested in GCMS analyses.[7] Although the effects of methylation on the biological activity of a number of PAH have been extensively investigated,[8] nothing is known about the methyl-CPP isomers. Structure–activity studies in progress require CPP and its methyl isomers in quantity, and we report here a convenient, large-scale synthesis of CPP (**1a**) and its 6-methyl (**1b**) and 8–methyl (**1c**) isomers.



1a. R = H, R_1 = H
1b. R = Me, R_1 = H
1c. R = H, R_1 = Me

Scheme I



Results and Discussion

Cyclopenta[*cd*]pyrene. Although synthesis of cyclopenta[*cd*]pyrene has been the focus of considerable attention, no route reported to date is readily applicable to large-scale synthesis. In particular, most strategies[9] require formation of the cyclopenta ring by Lewis acid catalyzed cyclization of 4-pyrenylacetic acid. This reaction is characterized by yields that are inconsistent and tend to decrease with increasing reaction scale. In seeking an alternative route, we wished to avoid this cyclization, since facile decarbonylation of 4-pyrenylacetic acid to a benzylic carbonium ion under acid conditions may account for the difficulty in optimizing this step. Key to the strategy (Scheme I) was cyclopenta ring formation via acid-catalyzed cyclization of (1,2,3,6,7,8-hexahydropyrenyl)acetic acid (**5b**), readily accessible from the commercially available starting compound 1,2,3,6,7,8–hexahydropyrene (**2**). Oxidation of **2** with CrO_3[10] or sodium dichromate[11] in benzene/acetic acid gave the 1-oxo intermediate **3** in yields of 40% and 37%, respectively. Compound **3** was condensed with the Wittig reagent[12] triethyl phosphonoacetate to give the olefinic ester **4** in 60% yield, which was hydrogenated over PtO_2 to yield quantitatively the corresponding hexahydropyrenyl acetate **5a**, from which the desired acid **5b** was obtained in 93% yield by basic hydrolysis.

The single-step oxidation of **2** with Cr^{VI} represents a considerable improvement over the reported[13] synthesis of **3** via a multistep route starting with naphthalene. An important advantage of oxidation by CrO_3 in Scheme I is that unreacted starting material can be conveniently re-

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