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The frontier orbital phase angles: a theoretical interpretation

B.W. Clare*

Department of Chemistry, The University of Western Australia, Nedlands, WA 6009, Australia

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Abstract

A pair of descriptors recently introduced to account for the activity of hallucinogenic phenethylamines has been shown to be a measure of the angles that the nodes of the frontier orbitals make with a reference direction in the molecule, in an approximation to the frontier orbitals of the molecule. The descriptors are referred to as the frontier orbital phase angles Θ_H and Θ_L, and are calculated with respect to a reference point on the benzene ring. The angle the node of the HOMO makes with the reference atom, measured at the center of the benzene ring is $\Theta_H + \pi/6$, and the angles the nodes in the LUMO make with the same atom are $\frac{(\Theta_L-\pi/6)}{2}$ and $\frac{(\Theta_L-5\pi/6)}{2}$.

The dependence of activity of a drug on Θ_H and Θ_L, as well as on the energy splitting undergone by the frontier orbitals of benzene in the formation of the drug, is an excellent illustration of the wave mechanical nature of the binding of a drug to its receptor, and should make a valuable contribution to the development of 3D-QSAR programs.

Keywords: Frontier orbital phase angle; Quantitative structure–activity relationship; Benzene; Hallucinogen; Receptor binding

1. Introduction

In a recent publication [1] a descriptor for quantitative structure–activity relationship (QSAR) calculations on benzene derivatives was proposed, and shown to be highly effective in correlating activities in humans of a large class of phenylalkylamine hallucinogens. The descriptor is based on the analogy of the frontier orbitals of the molecule in question to those of benzene and involves an analytical least squares fitting of the molecules frontier orbitals, calculated by any semiempirical or ab initio method to those rigorously calculated for unsubstituted benzene.

Both the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of benzene are degenerate, and each consists of two components that may be mixed in any proportion with normalization to form an infinity of equally acceptable frontier orbitals. In benzene itself, each of these mixtures is equivalent. When the benzene is substituted, the degeneracy is lifted, and each of the resulting, now separate orbitals may be regarded as being approximately derived from one particular linear combination of the original two components.

Considering the π orbitals of benzene only, and numbering the atoms consecutively around the ring, two particular orthogonal components of the HOMO were arbitrarily selected and designated $\mathbf{P_H}$, with coefficients of $p_z(\frac{1}{2\sqrt{3}}, -\frac{1}{2\sqrt{3}}, -\frac{1}{\sqrt{3}}, -\frac{1}{2\sqrt{3}}, \frac{1}{2\sqrt{3}}, \frac{1}{\sqrt{3}})$ and $\mathbf{Q_H}$ $(1/2, 1/2, 0, -1/2, -1/2, 0)$. The same was done for the LUMO, giving $\mathbf{P_L}$ $(-\frac{1}{2\sqrt{3}}, -\frac{1}{2\sqrt{3}}, \frac{1}{\sqrt{3}}, -\frac{1}{2\sqrt{3}}, -\frac{1}{2\sqrt{3}}, \frac{1}{\sqrt{3}})$ and $\mathbf{Q_L}$ $(1/2, -1/2, 0, 1/2, -1/2, 0)$. Orbitals with coefficients that are cyclical permutations of these will be referred to as **P**-like and **Q**-like.

* Fax: +61-8-9380-1005.
E-mail address: bwc@crystal.uwa.edu.au (B.W. Clare).

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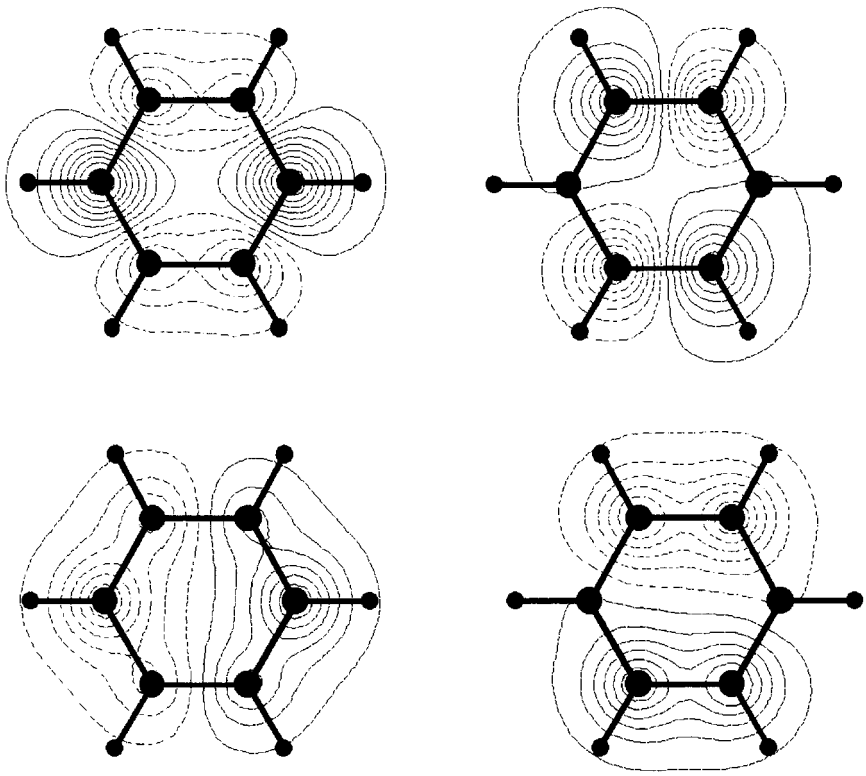

Fig. 1. Contour plot of the degenerate components **P** (left) and **Q** (right) of the HOMO (bottom) and LUMO (top) of benzene, calculated 0.5 Å above the plane of the ring. Dashed lines indicate negative phase. Orbitals were calculated by AM1 on AM1-optimized benzene.

Contour plots of **P**-like and **Q**-like orbitals for both components of both the HOMO and LUMO of benzene, drawn with the program Hyperchem [2], are shown in Fig. 1.

Any linear combination $C_p\mathbf{P_H} + C_q\mathbf{Q_H}$, such that $C_p^2 + C_q^2 = 1$, is an acceptable HOMO for benzene. This condition is satisfied by introducing an angular parameter Θ_H, such that $C_p = \cos\Theta_H$ and $C_q = \sin\Theta_H$. The other, orthogonal linear combination is $-\sin\Theta_H\mathbf{P_H} + \cos\Theta_H\mathbf{Q_H}$. Similarly, Θ_L is defined for the LUMO. To obtain the descriptors for a particular drug, the carbon atoms of the benzene ring are numbered 1–6 around the ring, starting at an atom that is consistent for the entire series of drugs. In the phenylalkylamines, this was the atom to which the ethylamine side chain was bonded. The molecule is oriented with the z axis normal to the ring, and a molecular orbital calculation is run. Then the coefficient of the p_z orbital, C_i for each carbon atom i of the benzene ring, for HOMO and LUMO, is obtained, and the value of Θ (both Θ_H and Θ_L) is found that minimizes the sum of squares: $\min(\alpha)$, where

$$\alpha = \sum_{i=1}^{6} (C_i - P_i \cos\Theta - Q_i \sin\Theta)^2 \quad (1)$$

This definition applies to both the HOMO and LUMO. This minimized sum of squares corresponds to the lack of fit between the nearest linear combinations of the degenerate HOMO and LUMO orbitals of benzene and the HOMO and LUMO of the compound of interest. The minimization can be achieved analytically by solving the equation

$$\frac{d\alpha}{d\Theta} = 0$$

with the following result.

Θ_H and Θ_L may be calculated from the orbital coefficients C_1–C_6, for both the HOMO and LUMO orbitals by putting $C = 1 + \Sigma C_i^2 = 2$, and, for the

HOMO putting $A = -C_1 - C_2 + C_4 + C_5$ and $B = -(C_1 - C_2 - 2C_3 - C_4 + C_5 + 2C_6)/\sqrt{3}$, and for the LUMO, putting $A = -C_1 + C_2 - C_4 + C_5$ and $B = (C_1 + C_2 - 2C_3 + C_4 + C_5 - 2C_6)/\sqrt{3}$. The sum of squares to be minimized is then $\alpha = C + A \sin\theta + B \cos\theta$. This expression can be converted by trigonometric identities to form $C + L \sin(\theta + d)$, where $d = \tan^{-1}(B/A)$ and $L = A/\cos d = B/\sin d$. The value of θ that minimizes this function is then obvious, and is denoted Θ_H for the HOMO, and Θ_L for the LUMO. The value of the objective function is given by $\alpha = C - A/\cos d = C - B/\sin d$.

It was shown [1] that functions of Θ_H and Θ_L correlate strongly with biological activity in the case of the phenylalkylamine hallucinogens. The definition of Θ_H and Θ_L is based on the idea that when benzene is substituted, the nondegenerate HOMO and LUMO of the resulting molecule approximate particular linear combinations of the degenerate HOMO and LUMO pairs, respectively, of benzene. This of course ignores contributions from p_z on any substituent atoms. It is also restricted, in that, in the linear combinations of the degenerate orbital pairs of benzene, the coefficients of diametrically opposite p_z orbitals must be equal in the case of the LUMO and equal and of opposite sign in the case of the HOMO. This is not generally true in the case of substituted benzenes. A measure of the lack of fit is the value of the sum of squares α in Eq. (1), for the optimized Θ. This is output by the program, and takes a value between 0 for perfect fit and 2 for the worst possible lack of fit.

The treatment described in Ref. [1] can be extended by modification of Eq. (1) by including a scale factor S:

$$\alpha = \sum_{i=1}^{6} (SC_i - P_i \cos\Theta - Q_i \sin\Theta)^2 \qquad (2)$$

One then has an equation with two variable parameters S and Θ, that may be varied to give a minimum sum of squares, by solving the simultaneous equations:

$$\frac{\partial\alpha}{\partial S} = 0, \qquad \frac{\partial\alpha}{\partial\Theta} = 0$$

This results in a set of four equations, two of which correspond to minima and two to maxima, and two to negative S and two to positive S, from which the appropriate expression can be chosen. The solutions are expressions in C_1–C_6 only, and are very complex. Interested readers may obtain them in the form of a FORTRAN program from the author via the Internet [3]. The equation gives Θ values identical to those from Eq. (1), and α values that are smaller, sometimes considerably so. The scale factor S is 1 or greater, and allows the computed orbitals to expand better to match those of benzene, thus allowing for the contributions to the orbital from atomic orbitals on atoms other than the six benzenoid carbons. This is useful when fitting ab initio results, with more than one set of p functions on each atom. In calculations of this type, it has been found that Θ_H and Θ_L calculated for 2p or 3p orbitals, while slightly different, agree usually to better than 1°, while α values are comparable with those obtained from Eq. (1) with one set of p orbitals per atom. Using Eq. (1) results in much larger α values when more than one sets of p orbitals are considered, because the sum of np_z contributions for each n is then only a fraction of the total sum of squares of atomic p_z orbital coefficients for that molecular orbital.

The purpose of the present contribution is to determine the molecular basis of the correlation found in the earlier work [1]. Thus, it is proposed to determine the relationship between the Θ descriptors and the angles that the nodes of the HOMO and LUMO orbitals of the approximation to the drug molecule make with the reference atom.

2. Calculations

Calculations were done using the symbolic mathematics program Mathematica [4] running on a Toshiba 4900 personal computer.

The calculations that follow are for benzene itself and are exact. The approximation involved in the concept is regarding the frontier orbitals of benzene as analogous to those of the compound of interest. A regular hexagon of carbon atoms of radius a is set up in the x, y plane, centered on the origin, with the atoms being labeled consecutively anticlockwise 1–6, starting with atom 1 on the positive x axis. Six approximately placed hydrogen atoms are also present. The coefficients of the linear combinations of orbitals of

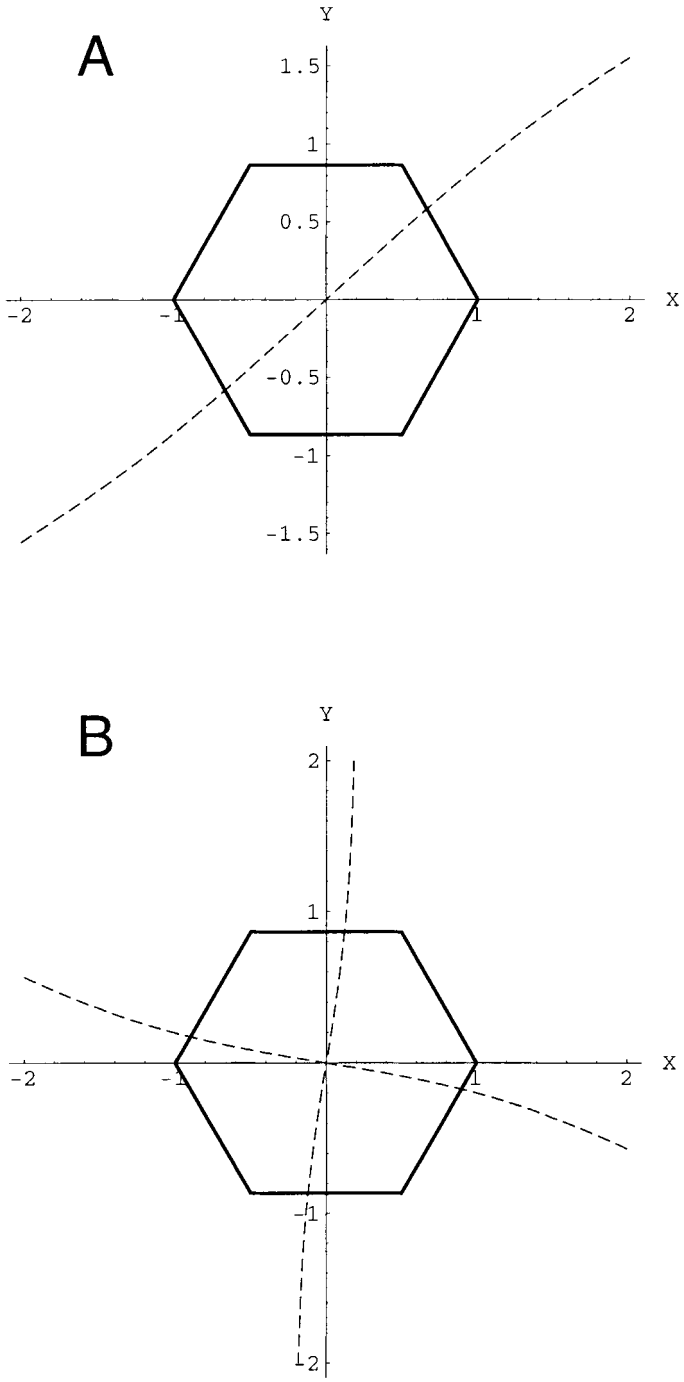

Fig. 2. A plot of the nodes (dashed) of the HOMO (A) and LUMO (B) of benzene, corresponding to Eqs. (3) and (5), with $a = 1$, $b = 1$, $z = 1$, $\zeta = 1$, and $\Theta_H = 0.2$ and $\Theta_L = 0.2$ (radians). The benzene ring is superimposed in bold.

interest are for the HOMO $\mathbf{P_H}\cos\Theta_H + \mathbf{Q_H}\sin\Theta_H$, and the corresponding expression for the LUMO, where **P** and **Q** are the vectors described above.

The HOMO and LUMO wavefunctions are expressed in terms of a single primitive Gaussian p_z atomic orbital function for each carbon atom of the benzene ring, with orbital exponent ζ and normalizing coefficient b (a function of ζ and the principal quantum number)

$$\phi_{p_z} = bz\,e^{-\zeta r^2}$$

For the specific HOMO corresponding to Θ_H the sum of the six of these functions, one for each carbon, reduces to:

$$\begin{aligned}\psi_H = \tfrac{1}{6}b\,e^{-\zeta(a^2+2ax+x^2+\sqrt{3}ay+y^2+z^2)}z[\sqrt{3}(e^{ax\zeta} + 2\,e^{3ax\zeta} \\ - e^{\sqrt{3}ay\zeta} + e^{a\zeta(4x+\sqrt{3}y)} - 2\,e^{a\zeta(x+2\sqrt{3}y)} \\ - e^{a\zeta(3x+2\sqrt{3}y)})\cos\Theta_H + 3(-e^{ax\zeta} - e^{\sqrt{3}ay\zeta} \\ + e^{a\zeta(4x+\sqrt{3}y)} + e^{a\zeta(3x+2\sqrt{3}y)})\sin\Theta_H] \qquad (3)\end{aligned}$$

A plot of the equation $\psi_H = 0$, implicit in x and y, for $a = 1$, $b = 1$, $z = 1$, $\zeta = 1$ and $\Theta_H = 0.2$ is shown in Fig. 2A. It may be seen that the node is nonlinear. Setting $\psi_H = 0$, implicitly differentiating and solving for dy/dx gives the expression:

$$\begin{aligned}\frac{dy}{dx} = \{\sqrt{3}[a(-e^{ax\zeta} + 2\,e^{3ax\zeta} + 2\,e^{\sqrt{3}ay\zeta} + 2\,e^{a\zeta(4x+\sqrt{3}y)} \\ + 2\,e^{a\zeta(x+2\sqrt{3}y)} - e^{a\zeta(3x+2\sqrt{3}y)}) - 2(e^{ax\zeta} + 2\,e^{3ax\zeta} \\ - e^{\sqrt{3}ay\zeta} + e^{a\zeta(4x+\sqrt{3}y)} - 2\,e^{a\zeta(x+2\sqrt{3}y)} \\ - e^{a\zeta(3x+2\sqrt{3}y)})x]\cos\Theta_H + 3[a(e^{ax\zeta} + 2\,e^{\sqrt{3}ay\zeta} \\ + 2\,e^{a\zeta(4x+\sqrt{3}y)} + e^{a\zeta(3x+2\sqrt{3}y)}) + 2(e^{ax\zeta} + e^{\sqrt{3}ay\zeta} \\ - e^{a\zeta(4x+\sqrt{3}y)} - e^{-a\zeta(3x+2\sqrt{3}y)})x]\sin\Theta_H\}/\{[3a\,e^{ax\zeta} \\ \times(1 + 2\,e^{2ax\zeta} + 2\,e^{2\sqrt{3}ay\zeta} + e^{2a\zeta(x+\sqrt{3}y)}) \\ + 2\sqrt{3}(e^{ax\zeta} + 2\,e^{3ax\zeta} - e^{\sqrt{3}ay\zeta} + e^{a\zeta(4x+\sqrt{3}y)} \\ - 2\,e^{a\zeta(x+2\sqrt{3}y)} - e^{a\zeta(3x+2\sqrt{3}y)})y]\cos\Theta_H \\ - 3[\sqrt{3}a(e^{ax\zeta} + e^{a\zeta(3x+2\sqrt{3}y)}) + 2(e^{ax\zeta} + e^{\sqrt{3}ay\zeta}) \\ - e^{a\zeta(4x+\sqrt{3}y)} - e^{a\zeta(3x+2\sqrt{3}y)})y]\sin\Theta_H\} \qquad (4)\end{aligned}$$

To obtain the slope of the node at the origin (the center of the benzene ring) we simply evaluate this expression for $x = 0$, $y = 0$, and obtain $dy/dx = \tan(\Theta_H + \pi/6)$. Thus the angle the node makes with the vector from the origin to atom 1 is $\Theta_H + \pi/6$.

For the specific LUMO corresponding to Θ_L we have:

$$\begin{aligned}\psi_L = \tfrac{1}{6}b\,e^{-\zeta(a^2+2ax+2x^2+\sqrt{3}ay+y^2)}z[-\sqrt{3}(e^{ax\zeta} - 2\,e^{3ax\zeta} \\ + e^{\sqrt{3}ay\zeta} + e^{a\zeta(4x+\sqrt{3}y)} - 2\,e^{a\zeta(x+2\sqrt{3}y)} \\ + e^{a\zeta(3x+2\sqrt{3}y)})\cos\Theta_L + 3(-e^{ax\zeta} + e^{\sqrt{3}ay\zeta} \\ + e^{a\zeta(4x+\sqrt{3}y)} - e^{a\zeta(3x+2\sqrt{3}y)})\sin\Theta_L] \qquad (5)\end{aligned}$$

As for the HOMO, the equation $\psi_L = 0$ for $a = 1$, $b = 1$, $z = 1$, $\zeta = 1$ and $\Theta_L = 0.2$, implicit in x and y, is plotted in Fig. 2B. It may be seen that there are two nodes, intersecting at the origin. Setting $\psi_L = 0$, and solving for y gives the expression:

$$\begin{aligned}y = \frac{1}{\sqrt{3}a\zeta}\log\{-[e^{-ax\zeta}(-\cos\Theta_L - e^{4ax\zeta}\cos\Theta_L \\ + \sqrt{3}\sin\Theta_L + \sqrt{3}\,e^{4ax\zeta}\sin\Theta_L \\ \pm \sqrt{A})]/[2(2\cos\Theta_L - e^{2ax\zeta}\cos\Theta_L \\ - \sqrt{3}\,e^{2ax\zeta}\sin\Theta_L)]\} \qquad (6)\end{aligned}$$

where

$$\begin{aligned}A = -4\,e^{2ax\zeta}(\cos\Theta_L - 2\,e^{2ax\zeta}\cos\Theta_L + \sqrt{3}\sin\Theta_L) \\ \times(-2\cos\Theta_L + e^{2ax\zeta}\cos\Theta_L + \sqrt{3}\,e^{2ax\zeta}\sin\Theta_L) \\ + (\cos\Theta_L + e^{4ax\zeta}\cos\Theta_L - \sqrt{3}\sin\Theta_L \\ - \sqrt{3}\,e^{4ax\zeta}\sin\Theta_L)^2\end{aligned}$$

Differentiating this expression with respect to x gives an equation that is indeterminate at the origin. However, taking the limit of the derivative as x approaches zero gives a result that depends on Θ_L

only:

$$\frac{dy}{dx} = \{ \pm 2(\cos \Theta_L - \sqrt{3} \sin \Theta_L) + (\sqrt{3} \cos 2\Theta_L - \sin 2\Theta_L)\}/\{\cos \Theta_L - \sqrt{3} \sin \Theta_L\}^2 \quad (7)$$

This simplifies to $dy/dx = \tan \frac{1}{2(\Theta_L - \pi/6)}$ and $dy/dx = \tan \frac{1}{2(\Theta_L - 5\pi/6)}$, thus giving two nodes that are perpendicular to each other at the origin, and which make angles of $\frac{1}{2(\Theta_L - \pi/6)}$ and $\frac{1}{2(\Theta_L - 5\pi/6)}$ with atom 1, measured at the origin. The second solution for y yields the same two results.

3. Discussion

Because the expressions for the gradients of the nodes of the HOMO and LUMO orbitals at the origin do not involve b or ζ, these results apply to all possible primitive Gaussians, and thus to all linear combinations of them, and so are independent of basis set or level of theory, and are a purely geometric property of the benzene molecule. In benzene itself, the nodal angles are not localized in any direction. In the substituted benzene, this is no longer so, and the nodal angles of the substituted benzene are approximated by the expressions derived above. That the parameter a does not appear in the result indicates that the result applies to any regular hexagon of C and H atoms, including an optimized benzene structure, which is the structure of interest.

The results are also independent of the level of z at which the section is taken. It may be seen from Fig. 2 that the nodes of the linear combinations of orbitals are in general nonplanar, and that for the LUMO the bisectors of the internodal angles are not equivalent. Thus, the nodal surface is that traced out by a line normal to the aromatic molecule moving in a curve in the plane of the molecule. In the case of QSAR studies, there will be an optimum Θ_H in the range 0–π. There will in general be two nonequivalent minima for Θ_L in this range, but for many purposes it will be sufficient not to distinguish between these, and to consider Θ_L defined on the range 0–π/2. The dependence of activity on Θ_H and Θ_L is thus expected to follow a periodic function with two maxima on the unit circle for the HOMO and four for the LUMO. As a first approximation, we can use the sin and cos trigonometric functions, of twice Θ_H in the case of the HOMO and four times Θ_L in the case of the LUMO. In addition, functions of $2\Theta_L$ can be used, to allow for the fact that the two LUMO internodal bisectors are not equivalent. The use of a sum of sin and cos functions allows, by trigonometric identities, the optimum angle to take any value. Regressions can then be carried out on $\sin 2\Theta_H$, $\cos 2\Theta_H$, $\sin 2\Theta_L$, $\cos 2\Theta_L$, $\sin 4\Theta_L$ and $\cos 4\Theta_L$. This will allow for an optimum in the range 0–π for the HOMO, and in the range 0–π/2 for the LUMO, at which angles the nodes of the HOMO and LUMO of the drug, best align with those of the presumed aromatic binding site on the receptor. In interpreting the regressions, if one of the sin/cos function pairs is statistically significant, the other should also be retained even if not formally significant. Statistical non-significance does not imply that the maximum likelihood value of the coefficient is zero. It remains for the statistics of the fit to determine whether the HOMO, the LUMO or both are involved in the interaction.

The phase angles Θ_H and Θ_L themselves are obtained from a calculation on the molecule of interest rather than benzene, and so are basis set dependent. In retrospect, it would have been preferable to define **P** and **Q** so that Θ_H and $\frac{1}{2\Theta_L}$ were the angles made by the nodes with atom 1, rather than differing from these angles by $\frac{\pi}{6}$ and $\frac{\pi}{12}$. The angles given by the second program, described above [3], conform to this.

Renumbering the benzene ring atoms in the opposite sense yields the negative of the nodal angles. This in the absence of a mirror plane through carbons 1 and 4 will not be equivalent to the original numbering, and if the substituents on carbons 2, 3, 5 and 6 have significant interactions with the receptor, one of these numberings will be preferred over the other in any particular compound. This is true for substituent based QSAR in benzene derivatives in general, and has not usually been taken into account in QSAR studies.

Related to Θ_H and Θ_L are the degree to which the degenerate levels of benzene are split when the benzene is substituted, Δ_H and Δ_L. These are given by $\Delta_H = E_H - E_{SH}$ and $\Delta_L = E_{SL} - E_L$, where E_{SH}, E_H, E_L, and E_{SL} are the second highest and highest occupied, and lowest and second lowest unoccupied π orbital energies, respectively. Correlations of Δ_H

and Δ_L (as well as Θ_H and Θ_L) with activity have been found with two series of drugs based on benzene, namely the phenylalkylamine hallucinogens [1] and inhibitors of the enzyme trypsin [5]. It is reasonable to expect such correlations if the splitting gives rise to a dependence on the angle descriptors. The quantities Δ_H and Δ_L are related by Koopman's Theorem to the Pearson hardness of the corresponding radical cation and anion, respectively, just as $E_L - E_H$ is related to the hardness of the molecule [6]. The larger Δ_H and Δ_L, the greater will be the difficulty in distorting the nodal angles Θ_H and Θ_L to accommodate those of an approaching π orbital system. At the same time, it must be recognized that if Δ_H or Δ_L is small, and there is a favorable orientation for interaction of the HOMO or LUMO for strong interaction, there will be an orbital with an unfavorable orientation lying just below it. Thus it is to be expected that a strong dependence of activity on Θ_H and Θ_L will occur for compounds in which Δ_H and Δ_L are large.

It is plausible that the strongest interaction between the π electron system of a drug and a similar system on the bioreceptor will occur when the nodes of the HOMO and/or LUMO of the drug most nearly coincide with nodes of similar orbitals on some part of the receptor. The HOMO of the drug molecule interacts with the HOMO of part of the receptor, giving two orbitals in the complex with energies higher and lower than those of either of the components. A similar interaction occurs with the LUMO, thus leading to a reduced HOMO–LUMO gap in the complex, relative to its components.

In using the programs, a warning that the underlying assumptions are not met is given by α, the minimized sum of squares. This is usually very small, but may occasionally exceed 0.2, especially when Eq. (1) is used. The phase angle calculation may also be run on the SHOMO or SLUMO coefficients. This usually results in a Θ at very nearly 90° to the corresponding HOMO or LUMO, as one would expect if the two orbitals were derived from an orthogonal degenerate pair from benzene. When it does not, the α value is usually large. This means that the corresponding frontier orbitals of the molecule are not well approximated by the degenerate orbitals of benzene. Although caution should be exercised in such cases, such points have not usually been found to be outliers in QSAR studies.

The treatment given here is for the particularly simple case of benzene. It does not easily generalize to other aromatic systems. It is however possible to calculate the π molecular orbitals of such systems, and so to obtain graphically the nodes of these orbitals, using a program such as Hyperchem [2]. For each such system, it should be possible to set up a system of coordinates in which to express the nodal angles and so to obtain similar correlations. In general, both the position and direction of the nodes will be important. It is not so clear what is the meaning of Δ_H and Δ_L in these cases, if any.

The importance of orbital symmetry in the interactions of atoms to form molecules has long been known. It seems that this is directly transferable to the association of molecules in pharmacology, at least insofar as π orbitals are involved. Many QSAR studies on aromatic molecules have involved E_H, E_L or their sum or difference as descriptors. Any of these studies could benefit from consideration of the nodal angles, especially if the aromatic moiety is benzene. Whether the method can be adapted to non-benzenoid aromatics is yet to be demonstrated.

The dependence of activity on the variables discussed in this paper is perhaps the best indication yet of the essential quantum mechanical nature of drug–receptor interactions. Conventional 3D-QSAR programs employ classical interactions, such as coulombic charge–charge forces and empirical van der Waals interactions. Such programs may benefit from the incorporation of π orbital wave mechanical interactions such as those discussed herein.

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