Quantitative Structure–Activity Relationship Analysis of Phencyclidine Derivatives. I

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Quantitative structure–activity relationship analysis has been accomplished on 24 derivatives of phencyclidine (PCP). By analysis with conceivable parameters effecting the variation of activity, it was shown that a compound with a smaller dipole moment, larger hydrophobicity, and a smaller principal moment of inertia is a stronger ligand of the receptor.

By further examination of this fact, the direction of the dipole vector of the ligand molecule was demonstrated to be important for the activity. Consequently, an equation, which sufficiently explains the variation of the activity, was derived using the difference in direction of the dipole vector as the only parameter. This is the first quantitative analysis explaining the variation of activity of PCP derivatives.

Keywords phencyclidine; QSAR; regression analysis; AM1 method; dipole moment; PCP derivative; physicochemical property

Although phencyclidine [PCP, 1-(1-phenylcyclohexy1)-piperidine (1)] was developed as an excellent anesthetic, its clinical use was discontinued because of psychomotor side effects during convalescence. However, since the undesirable symptoms induced by PCP are restorable by ordinary drugs for schizophrenia, an antagonist of PCP is expected to be a psychopathic new remedy.1)

Many PCP analogs have been synthesized and studied concerning their biological activities in connection with their structural features.2–4) However, no quantitative analysis has been done to explain the reason for the variation of activity of PCP derivatives. Therefore, it was deemed worthwhile for precise understanding of the mechanism of drug action to express the structural effect numerically.

We analyzed the quantitative structure–activity relationships (QSAR) of PCP derivatives which revealed a good correlation between the direction of the dipole vector of the ligand molecule and the binding affinity for the receptor.

Calculation Method

Biological Activity Data The published data concerning 24 PCP derivatives, which were synthesized and measured biological activities by Kamenga et al., were used.5–7) The pattern of chemical substitution and the biological activity of each compound are shown in Table I. The activity is expressed as the logarithm of the reciprocal concentration of a compound required to substitute 50% of [1H]PCP bound to its receptor, and a larger number means the higher binding ability of the compound.

Physicochemical Parameters In general QSAR analysis, the pharmacological property of a compound is expressed by the sum of substituent effects on a basic structure. However, the PCP derivatives discussed in this paper have too many substitution sites compared to the variety of substituents; therefore, parameters expressing the property of the whole molecule were devised as described below and were used instead of the usual substituent constants.

Dipole moment, ionization potential and the net atomic charge of the nitrogen atom of the piperidine ring were estimated by molecular orbital calculations and were regarded as the parameters depicting the electronic properties. Furthermore, molecular van der Waals (VDW) volume and VDW surface area were calculated on the basis of the structure optimized by the molecular orbital calculations and used as the steric parameters.

The calculations of the volume and the surface area were carried out using the MOLSV program by Smith.7)

Moment of inertia and length of the principal ellipsoidal axis were adopted as the structure related parameters. The principal moments of inertia were determined by diagonalization of a matrix constructed by three-dimensional coordinates and weights of the constituting atoms in a molecule. Then, the molecule was rotated to coincide these principal moments of inertia with z-, y-, and x-axis in the order of magnitude. Finally, the length of the principal ellipsoidal axis was calculated by the projection of the VDW surface onto these three axes.6)

It is known that hydrophobicity plays an important role in the action of drugs, and log P, the logarithm of the partition coefficient between n-octanol and water, often used in QSAR analysis. We used log P estimated by the fragment method of Ghose et al.5) In this method, a molecule is divided into fragments according to atom types, and the molecular log P is calculated by the sum of the fragment contribution.

All physicochemical parameters considered in the QSAR analysis are summarized in Table II.

Molecular Orbital Calculations The AM1 method, one of the semi-empirical molecular orbital models developed by Dewar et al.,8) was employed. We assumed all compounds are in the bioactive conformation9,10) regardless of the stability,11) and the starting structure (Fig. 1) was constructed using standard geometries with Dreiding models. This was followed by calculations in which all flexibility, except for the planarity of the phenyl ring, was optimized.

Statistical Calculations Multiple regression analysis using the physicochemical parameters in Table II as the explanatory variables and the biological activity as the criterion variable was executed. Selection of the explanatory variables was achieved by the stepwise method on the basis of the variance ratio (F), and the best correlated equation was searched. A program package for statistical analyses by Tanaka et al.12) was used for multiple regression analysis.

The molecular orbital calculations were executed on a HITAC M-680H at the Computer Center of the Institute for Molecular Science. All other calculations were carried out on a personal computer NEC PC-9801.

Results and Discussion

Analysis by Physicochemical Parameters Equation 1, shown below, was obtained by multiple regression analysis of 24 PCP derivatives,

\[ \log(1/K_d) = -0.322DM + 0.604LOGP - 0.102MIZ + 6.150 \]

\[ (r = 0.219) \quad (\pm 0.403) \quad (\pm 0.074) \quad (\pm 2.193) \]

\[ (n = 24, r = 0.808, s = 0.548, F = 12.556) \]

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TABLE I. Parameter Values and Observed and Calculated \( \log(1/K_3) \) of PCP Derivatives

<table>
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<tr>
<th>No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>log(1/K₃)</th>
<th>DM</th>
<th>LOGP</th>
<th>MIZ</th>
<th>log(1/K₃)</th>
<th>DV_{angle}</th>
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<td>H</td>
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</table>

Whereas \( n \) is the number of compounds, \( r \) is the correlation coefficient, \( s \) is the standard deviation, \( P \) is the variance ratio, and the figures in parentheses are the 95% confidence intervals. Both equations in this paper represent the best correlation, and no problematic collinearity in the squared cross-correlation matrix of the parameters was recognized. The parameter values, together with the calculated values of \( \log(1/K_3) \), are listed in Table I.

Equation 1 predicts that a compound with smaller dipole moment, considerable hydrophobicity, and a smaller first component of moment of inertia would have a stronger affinity for the receptor. The negative coefficient of a dipole moment is consistent with the low activity of the nitro derivatives which have a large dipole moment. The positive sign of the partition coefficient may be a reflection of the general high activity of methyl derivatives. However, the activity of the polar compounds varies remarkably. Although ca. 65% of the variation of the activity was explained by Eq. 1, it is not a sufficient result as not so many samples were taken into consideration. Since Eq. 1 was the best equation derived using the parameters in Table II, another possibility was explored to parameterize unexplained molecular properties.

**Analysis with the Direction of the Dipole Vector**

The size of the dipole moment (DM) was significant in Eq. 1. Being a vector quantity, the dipole moment includes both the size and the direction. Similarly, LOGP can be considered the expression of a balance between the electrostatic property and the steric extent of the molecule. Moreover, MIZ is an expression of a type of molecular dimension. The significance of these three terms, therefore, suggests that some kind of molecular balance or some unknown directionality is important for the effective binding of the PCP derivatives. In fact, the activity of PCP derivatives varies remarkably when a substituent exists on different positions. Hence, it is interesting to parameterize such directional differences.

The dipole vector was calculated by the AM1 method fixing all of the compounds in the biologically active conformation. As shown by a few examples (Fig. 2), the dipole vector of each compound is oriented differently. Accordingly, the correlation of the direction of the dipole vector with the activity was inspected. The vector of the most potent compound (m-OH-PCP, 4) was tentatively chosen as the standard axis.

The angle between the standard axis and the dipole vector of a trial molecule measured in radian was denoted by \( DV_{angle} \) whose values are shown in Table I. A QSAR
Fig. 2. A Few Examples of Dipole Vector of PCP Derivatives (a) m-OH-PCP (4), (b) PCP (1), and (c) m-NO₂-PCP (6).
The dipole vector of m-OH-PCP (4) was chosen as the standard axis and is shown by the dotted arrow.

Fig. 3. Linear Relation between Observed log(1/Kd) and DV\text{angle}.

The analysis with DV\text{angle} as the only parameter gave a well-correlated equation:

\[
\log(1/K_d) = -1.221 DV\text{angle} + 7.292 \\
(\pm 0.240) \\
(n = 24, r = 0.913, s = 0.361, F = 109.756)
\]

No further improvement was obtained by the addition of the size of the dipole moment (DM) to the analysis. In Fig. 3 the observed value of log(1/Kd) is plotted against DV\text{angle}.

It is obvious that the compounds with a dipole vector similarly oriented to the standard axis exhibit a stronger affinity for the PCP receptor. This would be interpreted as follows.

Manallack and coworkers proposed a receptor model for PCP-like drugs belonging to several chemical groups.⁹ At the same time, they pointed out that a phenyl ring and a basic nitrogen are common elements of the PCP-like drugs and that these groups anchor the drugs in the receptor site. Carroll et al.¹⁰ and Kamenka and Geneste⁹ suggested that the biologically active conformation of PCP is the one with an axial phenyl and an equatorial piperidine group as shown in Fig. 1. Consequently, all PCP derivatives discussed here must bind to the same site of the receptor in the same direction.

When a ligand enters into the electronic environment of the receptor cavity, a compound with an electronic field as complementary as possible to the receptor is favorable. In other words, the strongest interaction occurs when the charge density around a molecule is identical, but in the opposite sign, with that of the receptor cavity. Furthermore, the dipole moment is referred to as the outcome of the intramolecular electrostatic distribution, and it effects the electrostatic circumstance around the molecule. Therefore, it is conceivable that strong ligands have a similar electrostatic character.¹³

We revealed that the binding affinity of PCP derivatives is strongly related to the direction of the dipole vector, and as far as we know, the present analysis provides the first quantitative results revealing the source of the variation in biological activity of PCP derivatives.

Acknowledgement The authors are indebted to Professor T. Nabeshima (Nagoya University) for drawing their attention to this problem.

References
5) G. M. Smith, MOLSV program (QCPE #509), A modified version for the PC-9801 personal computer by T. Nagao (Hakodate Technical College) was used.
10) F. I. Carroll, G. A. Brine, K. G. Boldt, S. W. Mascarella, C. G.

11) Each compound discussed in this paper is in the global minimum conformation or within 1.5 kcal mol⁻¹ of it. The binding conformation should not necessarily be the global minimum, because even if the binding conformation is unstable, stabilization by intermolecular interaction with the receptor can be compensated for the energy for unfavorable conformational change. (C. Tosi, R. Fusco, and L. Caccianotti, J. Mol. Struct. (THEOCHEM), 183, 361 (1989)).
