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On Some Problems in Quantum Pharmacology I. The Partition Functions

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Abstract

We performed an analysis of the drug–receptor equilibrium constant, $K_i = \{Q_{D_iR} Q_{D_i}^{-1} Q_R^{-1}\} \exp(-\Delta\varepsilon_i/kT)$. It is shown that, for a group of nonrotating molecules, we may consider the product of the partition functions as constant if log(mass) = constant for all the molecules.

1. Introduction

One of the techniques employed in the study of quantitative structure–activity relationships of biologically active molecules employs the expression [1–6]:

$$\log K_i = a + \sum_p (b_p Q_p + c_p S_p^E + d_p S_p^N), \tag{1}$$

where K_i is an equilibrium constant, Q_p, S_p^E, and S_p^N are, respectively, the net charge, the electrophilic superdelocalizability, and the nucleophilic superdelocalizability of atom p in the drug; a, b_p, c_p, and d_p are constants, and the summation is over all the atoms that interact with the receptor. The index i refers to the ith molecule in a group under study. Equation (1) has been derived from the classical expression relating the equilibrium constant to the partition functions and therefore has a big advantage over other analogous formulas (i.e., Hansch analysis)—it is a mathematical equality in spite of the approximations made to obtain it. If we use the appropriate statistical methods to fit Eq. (1), the information we obtain may be considered more realistic than another kind of analysis.

Until today, no one has presented a careful analysis of the approximations made to obtain Eq. (1). More specifically, there is no reason, as some authors do, to consider the quotient of the partition functions as a constant in a given group of molecules interacting with the same receptor [1–3].

In this work we analyze the partition functions and we fix the conditions to consider them as constants. This should lead to an optimum employ of Eq. (1).

2. The Fundamental Equation

Let us consider the state of thermodynamic equilibrium, and a 1:1 stoichiometry in the formation of the drug–receptor complex:

$$D_i + R \rightleftharpoons D_iR, \tag{2}$$

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where D_i is the drug, R is the receptor, and D_iR is the drug–receptor complex. Most drug receptors are proteins and we shall concentrate our discussion on them, accepting that mass$(D_i) \ll$ mass (R) and that the receptor conformation is so strongly preferred that the binding energy of the ligand is accounted for entirely in terms of local atomic interactions. The thermodynamical hypothesis is valid only if weak intermolecular forces mediate in the complex formation.

The equilibrium constant for Eq. (2) is [7]

$$K_i = (Q_{D_iR}/Q_{D_i}Q_R) \exp(-\Delta\varepsilon_0^i/kT), \tag{3}$$

where $\Delta\varepsilon_0^i$ is the difference between the ground-state energy of D_iR and the energies of the ground state of D_i and R:

$$\Delta\varepsilon_0^i = \varepsilon_{D_iR} - (\varepsilon_{D_i} + \varepsilon_R), \tag{4}$$

and the Q's are the total partition functions measured from the ground state (in solution). T and k are the temperature and the Boltzmann constant, respectively.

In a logarithmic form, we have

$$\log K_i = \log(Q_{D_iR}/Q_{D_i}Q_R) - (A/T)\Delta\varepsilon_0^i, \tag{5}$$

where $A = 1.36789 \times 10^5$ (with the energies measured in a.u. and T in °K).

Normally, the first term of the right-hand side of Eq. (5) is considered to be constant along a group of molecules. In Sec. 3 we shall analyze the conditions that make this supposition valid.

3. The Partition Function

The complete molecular partition function (PF) is

$$Q = Q^{\text{trans}}\left[g_0^{(e)}Q^{(v,r)_0} + \sum_{p=1} g_j^{(e)}Q^{(v,r)}j \exp\left(\frac{-\Delta\varepsilon_j}{kT}\right)\right], \tag{6}$$

where $\Delta\varepsilon_j = \varepsilon_j - \varepsilon_0$, Q^{trans} is the translational PF, $Q^{(v,r)}$ are the rotation–vibration PF, and the g_i's are the degeneracies of the different levels.

Having in mind that for practically all polyatomic molecules, the Boltzmann factors of the excited electronic states are negligible compared to those of the ground state (exceptions are some free radicals, NO_2 and ClO_2) [8], we may consider only the electronic ground state in the PF. Therefore we have

$$Q = Q^{\text{trans}}Q^{(v,r)_0}, \tag{7}$$

with $g_0^{(e)} = 1$.

Inserting Eq. (7) into Eq. (5), and rearranging we obtain:

$$\log K_i = \log\left(\frac{Q_{D_iR}^{\text{trans}}}{Q_{D_i}^{\text{trans}}Q_R^{\text{trans}}}\right) + \log\left(\frac{Q_{D_iR}^{(v,r)_0}}{Q_{D_i}^{(v,r)_0}Q_R^{(v,r)_0}}\right) - \left(\frac{A}{T}\right)\Delta\varepsilon_i. \tag{8}$$

The translational PF per unit volume is (Ref. 7, p. 97)

$$Q^{\text{trans}} = 3.20317 \times 10^{27} M^{3/2}T^{3/2}, \tag{9}$$

where M is the molecular weight (in amu) and T is the temperature in °K. With mass $(R) \simeq$ mass (D_iR), we have

$$\log\left(\frac{Q^{\text{trans}}_{D_iR}}{Q^{\text{trans}}_{D_i} Q^{\text{trans}}_{R}}\right) = -27.50558 - (\tfrac{3}{2}) \log M_{D_i} - \tfrac{3}{2} \log T. \tag{10}$$

In a first approach, we shall consider that the rotational and vibrational motions are independent and uncoupled, i.e., $Q^{(v,r)} = Q^{(v)} Q^{(r)}$. At the body temperature, we have $Q^{(v)_0} \simeq 1.0$ [9]. In the case of the rotational partition functions, we may distinguish two cases.

(a) The drug molecule is "well orientated" in the receptor's potential field, i.e., it does not rotate. We have in this case $Q^{(r)_0} = 1.0$.

(b) The molecule can rotate. In this case, and considering that $I_j(D_iR) \simeq I_i(R)$, where I_j is the inertia moment about the j axis, we have

$$\log\left(\frac{Q^{(r)_0}_{D_iR}}{Q^{(r)_0}_{D_i} Q^{(r)_0}_{R}}\right) = 1.82987 - \tfrac{3}{2} \log T + \log\left(\frac{\sigma_{D_i}}{(ABC)^{1/2}}\right), \tag{11}$$

where σ_{D_i} is the symmetry number of D_i and ABC is the product of the three moments of inertia about the three principal axes of rotation [7]. The units of T and the inertia moment are °K and amu · Å^2, respectively. The symmetry number is characteristic for each point group and is equal to the number of indistinguishable positions into which the molecule can be turned by simple rigid rotations.

Finally, we have for $T = 315\ °K$:

$$\log K_i = -33.17064 - 434.25079 \Delta\varepsilon_i - \tfrac{3}{2} \log M_{D_i} + \log\left[\sigma_{D_i}/(ABC)^{1/2}\right], \tag{12}$$

for the case where D_i rotates freely, and

$$\log K_i = -31.25304 - 434.25079 \Delta\varepsilon_i - \tfrac{3}{2} \log M_{D_i}, \tag{13}$$

if D_i does not rotate.

Some authors have considered the quotient of the partition functions of Eq. (3) as constant [1–4]. This is equivalent to writing

$$\sigma_{D_i}/M^{3/2}_{D_i} (ABC)^{1/2} = \text{constant}, \tag{14}$$

for the rotating molecule case, and

$$M_{D_i} = \text{constant}, \tag{15}$$

for the other case.

If the conditions [Eqs. (14) or (15)] are true, the variation of K_i in a group of molecules will depend only on the variation of $\Delta\varepsilon_i$. This seems to be true for the tetracyclines [1] and the monoamine oxydase inhibitors [2], but some results in phenethylamines [10] and narcotic analgesics [11] suggest that the molecular mass must be included as an independent variable in the statistical fitting of Eq. (1).

Therefore, if in a certain group of molecules conditions, Eq. (15) or Eq. (14), fail and the molecular mass is not included in the statistical analysis, this fact

must be reflected in equations with relatively low correlation coefficients and/or high standard deviation.

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