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Quantum Statistical Calculation for Correlation of Biological Activity and Chemical Structure. 1. Drug-Receptor Interactions

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Based on the theory of quantum statistics, a method is developed for the correlation of drug action and chemical structure. It is applied to the interaction of distinguishable biological receptors and in distinguishable drug molecules. Calculations for several local anesthetic drugs illustrate the usefulness of the method.

About 100 years ago Brown and Fraser[1] observed that a minor change in chemical structure could lead to a change in the biological effect of drugs. Since then chemists and pharmacologists[2] have encountered successes as well as failures in the qualitative studies of drug activity. Interest continues to grow among medicinal chemists[3] as the methods for studying the correlation of pharmacological effect and chemical structure improve. It is hoped that through the use of mathematical models a new way of designing new drugs can be achieved without exhaustive synthetic work and pharmacological screening.

There are two distinctly different approaches in the recent developments in the quantitative correlation of biological activity and chemical structure. In the first approach[4] a statistical method is applied to obtain parameters for establishing the correlation of biological activity data and free-energy-related physicochemical properties ascribed to the drug molecules. The second approach[5] adopts the concept of geometrically matching drug molecules and biological receptors through the use of the simplified molecular orbital calculations. In fact, these two methods account for only part of whole drug actions en route from drug dissolution to biological response, and any single action or multiple actions can be a rate-determinant step. Moreover, examples are given in this paper which show the limitations of these methods. In this paper, a method based on an entirely different approach is formulated.

Quantum statistics has been successfully applied to problems in solid-state physics and thermodynamics.[6] Examples of its successful applications include the theoretical calculation of chemical equilibrium constants and rates of chemical reactions. It is the author's intention to apply quantum statistics to medicinal chemistry in this first of a series of papers.

Theoretical Method. An assumption is made that a drug molecule must pass through a complex procedure, which involves one or more steps including among others dissolution, absorption, distribution, penetration, binding, metabolism, and excretion, en route from oral administration to the sites of drug action, in order to give a particular biological response. For simplicity the approximation is made that the probability of success at each step is independent of any other step. Hence, the rate of biological response can be expressed as

$$\frac{\mathrm{d(biological\ response)}}{\mathrm{d}t} = ACp^{a1}(\text{step 1}) \times p^{a2}(\text{step 2}) \times \ldots \times p^{an}(\text{step } n) \quad (1)$$

where p (step i) represents the probability of accomplishment of step i, where $i = 1, 2, \ldots, n$, C is the drug concentration, and A is the proportionality constant, which has the same unit as d(biological response)/Cdt. Equation 1 is a general expression but at present only two steps will be considered. In the first step, a drug molecule makes a Brownian-like motion from outside the cell to reach the receptor, and in the second step a binding mechanism between the receptor and the drug molecule is established. Then, eq 1 is reduced to eq 2.

$$\frac{\mathrm{d(response)}}{\mathrm{d}t} = ACp^{a1}(\text{Brownian})p^{a2}(\text{binding}) \quad (2)$$

The following derivation for p(binding) is restricted to a model in which the receptor sites are similar to atoms which are localized, hence distinguishable, on a lattice surface.† The drug molecules are movable and indistinguishable before binding occurs. The binding of a drug molecule on any one receptor site (or group of sites) is independent of the binding on the remaining sites.

Consider $q(s) = \Sigma_j \exp(-\epsilon_j(s)/kT)$ as the site partition function where s atoms of a drug molecule are bound to the site (or group of sites), k is the Boltzman constant, T is the absolute temperature, and ϵ_j is the energy level j of the system. If one defines the "absolute activity" $\lambda = e^{\mu/kT}$, where μ is the chemical potential, the grand partition function for the independent and distinguishable site is

$$\Xi(\lambda, M, T) = \xi(\lambda, T)^M \quad (3)$$

where

$$\xi = q(0) + q(1)\lambda + \ldots + q(m)\lambda^m = \sum_{s=0}^{m} q(s)\lambda^s \quad (4)$$

† For more information about this model, see pp 130–134 of ref 6.

Table I. Data for Local Anesthetic Compounds—Benzoates, Cinnamates, and Phenyl Propionate

Compd	Substituent	Wave number,[a] cm^{-1}	$\theta = hc\nu/2kT$[b]	Ln 1/C Obsd[a] ($C = ED_{50}$)	Ln 1/C Calcd Present	Ln 1/C Calcd Hansch[c]
	2-Diethylaminoethyl-Substituted Benzoate					
1	4-$N(CH_3)_2$	1697	4.07178	3.96	4.03	3.58
2	4-OCH_3	1708	4.09818	2.81	2.84	2.91
3	4-NH_2	1711	4.10537	2.59	2.52	2.17
4	4-Cl			2.42		2.32
5	4-OH	1714	4.11257	2.08	2.19	2.73
6	4-$NHCOCH_3$			0.63		1.05
7	Benzoate	1727	4.14376	0.51	0.79	
8	4-NO_2	1731	4.15336	0.30	0.36	0.03
	2-Diethylaminoethyl-Substituted Cinnamate and Phenyl Propinate					
9	4-Amino cinnamate	1710	4.10297	2.76	2.63	
10	4-Aminophenyl propionate	1725	4.13897	1.31	1.01	
11	4-Nitro cinnamate	1731	4.15336	0.42	0.36	

[a] Values were taken from ref 7. [b] $T = 300°K$. [c] Only seven compounds were used for Hansch's calculation: C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Amer. Chem. Soc.*, **85**, 2817 (1963); C. Hansch and A. R. Steward, *J. Med. Chem.*, **7**, 691 (1964); C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *ibid.*, **11**, 1 (1968); C. Hansch, A. R. Steward, and J. Iwasa, *J. Mol. Pharmacol.*, **1**, 87 (1965); S. Unger and C. Hansch, *J. Med. Chem.*, **16**, 745 (1973); T. Fujita, *ibid.*, **16**, 923 (1973). σ and π values were taken from ref 8. Ln $1/C = 1.089\pi - 2.67\sigma + 2.065$.

where M is the total available number of equivalent, independent, and distinguishable biological receptor sites (or groups of sites) to each of which s atoms ranging from 0 to m can be bound.

The probability of binding a set of receptor sites with a drug molecule is proportional to the average number of molecules per site (or group of sites), that is

$$p(\text{binding}) = \frac{B\lambda}{M}\left(\frac{\partial \ln \Xi}{\partial\lambda}\right)_{M,T} = B\lambda\left(\frac{\partial \ln \xi}{\partial\lambda}\right)_T = \frac{B\lambda}{\xi}\left(\frac{\partial\xi}{\partial\lambda}\right)_T \quad (5)$$

where B is a proportionality constant.

Theoretical derivation of p(Brownian)‡ will be published in the second paper of this series, partly because it involves a different type of quantum statistics and partly because p(Brownian) is not an important rate-determinant step for the examples shown in the present paper.

Application. If q_1 is the partition function for a functional group (or atom) of a drug molecule bound on a site of type 1 and q_2 for a site of type 2, and w is the potential energy between the two functional groups which are bound on different sites with different characteristics in nature, then the $q(s)$'s for the two-site binding are

$$q(0) = 1 \quad q(1) = q_1 + q_2 \quad q(2) = q_1q_2e^{-w/kT} \quad (6)$$

where k is the Boltzman constant, T is the absolute temperature, and eq 4 becomes

$$\xi = 1 + (q_1 + q_2)\lambda + q_1q_2e^{-w/kT}\lambda^2 \quad (7)$$

Hence

$$p(\text{binding}) = \frac{B[(q_1 + q_2)\lambda + 2q_1q_2e^{-w/kT}\lambda^2]}{1 + (q_1 + q_2)\lambda + q_1q_2e^{-w/kT}\lambda^2} \quad (8)$$

For special cases of one-site binding, the following equation is used

$$p(\text{binding}) = Bq\lambda/(1 + q\lambda) \quad (9)$$

which is similar to the Langmuir adsorption isotherm with $s = 0$ (empty site) or 1 (occupied site).

‡ This variable is found equivalent to Hansch's π value according to the principles of statistical mechanics.

We shall consider the series of effective local anesthetic drugs listed in Table I as an example for illustrating the use of eq 5. These compounds may be involved in two-site binding, one at the carbonyl group and the other at the amino group. However, the effects of the benzene substituent on the carbonyl group are much greater than that of the nitrogen. Therefore, the partition function of nitrogen is approximated as a constant from one substituent to another substituent. Physically, the carbonyl group may be regarded as a screen which absorbs the different electronic effects of the various substituents, especially the resonance effect of the benzene substituents through the transport of the π-electron delocalization. The effects on the nitrogen due to substituents on the benzene ring are essentially blocked at the carbonyl group. Therefore, the assumption of the constant partition function for nitrogen is physically reasonable, and the problem may be treated as a one-site binding. Although two-site binding (taking q_2 as constant for eq 8) leads to the same solution, eq 9 is applicable to this particular problem.

So far we have discussed the relation between biological response and the partition function q of the carbonyl group. Next, we shall derive an equation to express q by a set of spectroscopic data. Consider the Hamiltonian of this system as follows

$$\mathcal{H} = H_t + H_r + H_v + H_e + H_n \quad (10)$$

where t is translational, r is rotational, v is vibrational, e is electronic, and n is nuclear. If the eigenvalues and eigenfunctions of H_t, H_r, ..., are ϵ_t, ϵ_r, ..., and ψ_t, ψ_r, ..., respectively, and the total wave function is a single product $\phi = \psi_t\psi_r \ldots$, we have

$$\mathcal{H}_\phi = (H_t + H_r + \ldots)\psi_t\psi_r\ldots = \psi_r\ldots H_t\psi_t + \psi_t\ldots H_r\psi_r + \ldots = (\epsilon_t + \epsilon_r + \ldots)\phi = E\phi \quad (11)$$

hence $E = \epsilon_t + \epsilon_r + \ldots$. Since the total energy of the system is a sum over the subsystems, the partition function of the carbonyl group can be expressed as a product of all subsystems

$$q = q_tq_rq_vq_eq_n \quad (12)$$

Compared with the vibrational energy, the translational and rotational energies are very small, and therefore the contributions of ln q_t and ln q_r are negligible. In addition,

$q_e q_n$ is constant because the molecules are in ground electronic and nuclear states. Hence, q_v is the only variable in this case, and

$$q = aq_v \tag{13}$$

Normally, q_e (from uv spectroscopy) should be considered as a variable unless the functional group of a given molecule is practically unexcited, and the contribution for q_e is entirely from the energy of the ground electronic state. Now, q_v is expressed as an exponential sum over all vibrational energy levels of the ground electronic state.

$$q_v = \sum_{n=0}^{\infty} e^{-\epsilon_n/kT} \tag{14}$$

and

$$\epsilon_n = (n + \tfrac{1}{2})hc\nu \quad n = 0, 1, 2, \ldots \tag{15}$$

Substituting eq 15 in 14, we have

$$q_v = e^{-hc\nu/2kT}/(1 - e^{-hc\nu/kT}) \tag{16}$$

where ν is the wave number of the stretching vibrational mode of the carbonyl group, c is the speed of light, h is the Planck constant, and k is the Boltzman constant. For the carbonyl group at the regular temperature eq 16 can be approximated as

$$q_v = \exp(-hc\nu/2kT) \tag{17}$$

There is the coupling of vibrational states between the binding sites of receptor ν_1 and drug molecule ν_2 as indicated in Figure 1, and their energy states are

$$\epsilon_{n1} = (n + \tfrac{1}{2})hc[(1 - \lambda')\nu_1 + \lambda\nu_2]$$

$$\epsilon_{n2} = (n + \tfrac{1}{2})hc[(1 - \lambda)\nu_2 + \lambda'\nu_1]$$

and

$$\epsilon_n = \epsilon_{n1} + \epsilon_{n2} = (n + \tfrac{1}{2})hc\nu_1 + (n + \tfrac{1}{2})hc\nu_2 \tag{18}$$

hence

$$q_\nu = {q_{\nu 1}}^{r1} {q_{\nu 2}}^{r2} \tag{19}$$

Substitute eq 13, 17, and 19 in eq 9 and omit both the denominator and λ as an approximation obtaining

$$p(\text{binding}) = B \exp(-hc\nu/2kT) \tag{20}$$

Substituting eq 20 in the equation

$$\frac{\mathrm{d(response)}}{\mathrm{d}t} = \mathrm{ACP}^a(\text{binding}) = \text{constant} \tag{21}$$

we obtain

$$\ln 1/C = k_1 - k_2\theta \tag{22}$$

where $\theta = hc\nu/2kT$. Equation 22 is the final equation which is applicable for the anesthetic drugs listed in Table I. k_1 and k_2 are constants which are obtained by a regression method.

Results and Discussion

A set of infrared spectroscopic and biological data was taken from the work of Galinsky, *et al.*,[7] and a linear regression analysis was performed for the local anesthetic drugs with this experimental data to obtain the parameters k_1 and k_2 of eq 22. The results of the present method are summarized in Table I and eq 23

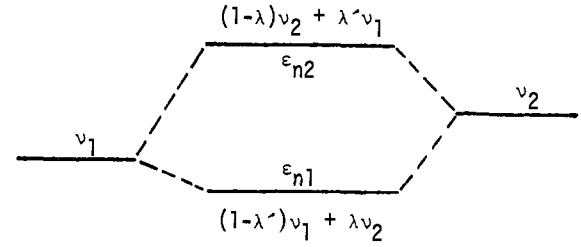
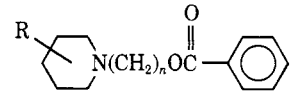


Figure 1. Coupling of two vibrational states.

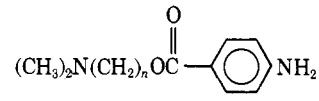
$$\ln 1/C = 186.967 - 44.928\theta \qquad \begin{matrix} r \\ 0.992 \end{matrix} \quad \begin{matrix} s \\ 0.156 \end{matrix} \tag{23}$$

where r is the correlation coefficient and s is the standard deviation. For the purpose of comparison, the results of the Hansch method[8] (ρ-σ-π analysis) are included in Table I. In order to test the significance of the Hansch parameters the same linear regression was performed to include π values, and the result showed that the addition of π did not improve the correlation coefficient in this case. From this observation the conclusion may be drawn that the penetration of the drug molecules through the cell wall or tissue is much easier than binding between the molecules and the receptors. Therefore, a focus on the improvement of binding ability instead of Hansch π values may result in the discovery of better local anesthetic drugs.

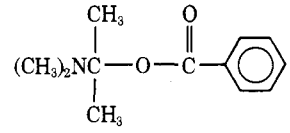
According to Carney's review[9] the following compounds



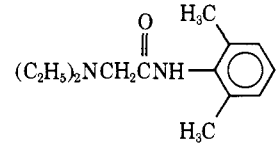
with various n's from 2 to 6 show local anesthetic activities, and according to Coubeils' and Pullman's calculations[10] the following compounds



where n = 2 and 3, and



show an optimum separation of 4.1-4.2 Å between the basic nitrogen and carbonyl oxygen atom. If the result of Coubeils' and Pullman's calculations can be applied to the compounds of Carney's review, the activities of the above-mentioned compounds are well explained by Kier's model.[11-15] However, Coubeils' and Pullman's calculations of lidocaine



show that the distance between the N^+ atom and the carbonyl oxygen is only 2.62 Å, which is in conflict with Kier's model.

The present correlation for the series of compounds listed in Table I does not include the q of the nitrogen atom because every compound in this series has the same $(C_2H_5)_2N(CH_2)_2^-$ group. Therefore, a constant q of the nitrogen is assumed. For other series of compounds with N-alkyl derivatives, the q of the nitrogen must be considered as variable, because heteroatoms are considered as active centers for binding with the receptors. However, the method does not take interatomic distance between heteroatoms into consideration at this moment.

The binding ability between the carbonyl group and the receptor depends on their coupling of vibrational states. Therefore, an alternate group with a stretching vibrational wave number around 1700 cm^{-1}, which has an electronic structure similar to that of the ester group (similar q_e), such as thiol esters, may also show the activities.

Finally, the toxicity effects, such as LD_{50}, must also be studied in order to establish an optimal equation which has positive as well as negative contributions. Generally, ED_{50} and LD_{50} have the same trend. Therefore, the effective drug must be the one for which several biological activities have been taken into consideration.

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Cycloalkanones. 3. Structure–Activity Relationships of Hypocholesterolemic Cyclooctanone Derivatives

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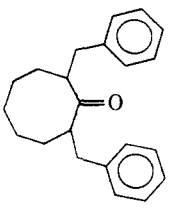
The structure-activity relationship (SAR) of a series of novel hypocholesterolemic agents related to 2,8-dibenzylcyclooctanone has been determined. Maximum lowering of cholesterol is obtained when an α,α'-dibenzyl-α,α'-disubstituted ketone system is present. Aromatic substitution has been studied in a successful attempt to eliminate the estrogenic side effect of the lead compound; 2,8-bis(4′-methylbenzyl)cyclooctanone retains some hypocholesterolemic activity and has little estrogenicity. The synthesis of 32 derivatives is described.

The hypocholesterolemic and antifertility activities of a series of dibenzylcycloalkanones have been previously reported.[1] The compounds reported here represent an extension of that work to determine the hypocholesterolemic and estrogenic activities of a series of derivatives of 2,8-dibenzylcyclooctanone (1). Four areas of the parent compound have been modified: the cyclooctane ring, the carbonyl function, the methylene side chain, and the aromatic nucleus.



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Experimental Section

Melting points were taken on a Mel-Temp apparatus and were corrected. Elemental analyses (Atlantic Microlab) indicated by element were correct within ±0.4%. Infrared and nmr spectra of all compounds were consistent with the assigned structure.

2,8-Bis(arylidene)cyclooctanones. General Procedure. A solution of 5 g (0.215 mol) of freshly cut Na in 125 ml of absolute EtOH was prepared in a 250-ml three-neck flask fitted with mechanical stirring and a Drierite protected reflux condenser. When the solution had cooled to room temperature, a mixture of 12.6 g (0.1 mol) of cyclooctanone and 0.2 mol of aldehyde was added in one portion. Absolute EtOH (5 ml) was used to rinse all of the mixture into the flask. An immediate rise in temperature was seen (usually ~10°). The mixture was allowed to stir several hours, the end being determined by successive tlc (silica G, benzene), since the bisylidene commonly moves ahead of all other materials. Reaction times were a few hours to several days at room temperature. At the conclusion of the reaction, the solid material was filtered and slurried with water to remove traces of base. Alternately, the gummy material was dissolved in benzene and extracted with water. After filtering or drying and solvent removal, the product was crystallized from 95% EtOH. Yields were typically 10–30% of the once crystallized product. More product remained in the liquor from the first filtration; however, the possible increase in yield did not justify the effort required to isolate more material. Table I lists the compounds prepared by this method.