Quantum-Chemical Structure-Activity Relationships in Carbamate Insecticides

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Abstract. A non-empirical Quantitative Structure-Activity Relationship (QSAR) method is employed to analyze the reversible complex formation during the reaction of phenyl-*N*-methylcarbamates with the enzyme acetylcholinesterase. No common equation for the *ortho*, *meta* and *para*-substituted molecules could be obtained. A good description of the reversible complex formation is achieved by separating the molecules according to the position of the aromatic substituent. The introduction of a substituent orientation parameter helps account for the percentage of molecules attaining the proper orientation to interact with their partner. This parameter is useful in describing physical effects depending on the rotational partition function. A model for the carbamate-acetylcholinesterase reversible complex is proposed.

Key words. Structure-activity relationships, acetylcholinesterase inhibitors, carbamate insecticides, static reactivity indices, orientational parameters, non-empirical QSAR.

Introduction

Phenyl-*N*-methylcarbamates (NMC, see Figure 1) act as insecticides by inhibiting the enzyme acetylcholinesterase (AChE) [1–3]. One of the steps in this reaction involves the formation of a 1:1 reversible complex [1–3]. The interest of these compounds as insecticides has led to the search for Structure-Activity Relationships (SAR) [4–7] which, in general, have been carried out with the use of so-called empirical methods [8].

In recent years we have been advocating the use of non-empirical Quantitative SAR (QSAR). Traditionally, empirical QSAR studies are based on the use of statistics to try to relate a given biological activity to all kinds of parameters (some of them belonging to different explanatory levels). This methodology is so deeply rooted that it seems difficult to envisage other approaches. A non-empirical method is based on a different philosophy: it begins by proposing a model to explain a given biological activity. This model receives a mathematical treatment in order to represent it by one or more equations. Next, by applying one or several physically-based approximations, manageable expressions are obtained. Here statistics is used, *not to see whether there is a structure-activity relationship, but to find the best one*. We have presented such a method in dealing with the equilibrium constants [9, 10]. The results of its application to different sets of molecules strongly suggest that this method is superior to the empirical ones [11, 12, and

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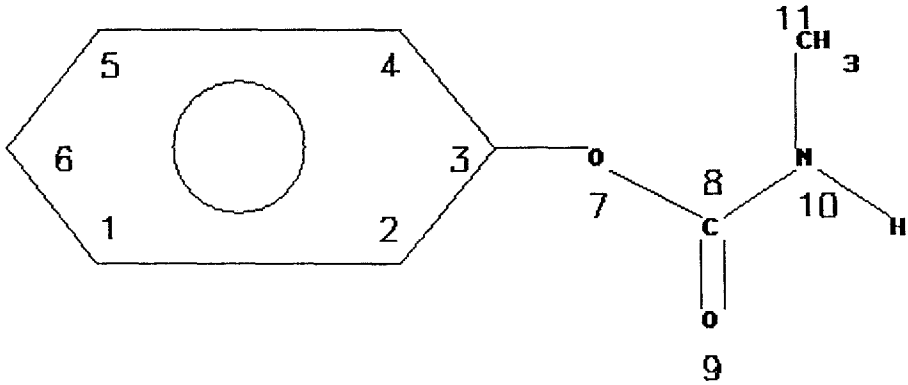

Fig. 1. Phenyl-*N*-methyl-carbamate showing the atom numbering for the common skeleton.

references therein]. This is not surprising, given the way in which non-empirical models are derived.

This paper presents the results of applying the above method to the study of reversible complex formation in the reaction of NMC with AChE. Also, we are interested in providing convincing quantitative evidence for the acceptance of a new orientational parameter for future QSAR studies.

Methods, Models and Calculations

As the method employed here has been discussed in great detail elsewhere [9, 10, 13], we shall now present only a general sketch. It has been shown that, for a thermodynamic equilibrium state and 1:1 stoichiometry, the equilibrium constant K can be expressed as:

$$\log K = a + b \log M_D + c \log \sigma_D + d \log(I_1 I_2 I_3)_D + e \Delta E \qquad (1)$$

where a, b, c, d and e are constants, D refers to the drug (NMC here) molecule, σ is the symmetry number, M the drug's molecular mass, $I_1 I_2 I_3$ is the product of the three moments of inertia about the three principal axes of rotation and ΔE is the NMC–AChE interaction energy. The model leading to Equation (1) is constructed supposing that: (a) the drug-receptor interaction is weak; (b) the receptor's conformation is so strongly preferred that the binding energy is accounted for entirely in terms of local atomic interactions; (c) the total molecular partition functions can be factorized in terms of independent and uncoupled translational, rotational, vibrational and electronic partition functions; and (d) only the electronic ground state is important in the electronic partition function.

The last term of Equation (1) can be evaluated through perturbation theory [10]. Here we shall employ the Klopman–Peradejordi–Gómez approach [10], in which ΔE is expressed as:

$$\Delta E = W + \sum_i [E_i Q_i + F_i S_i^E + G_i S_i^N] + \sum_i \sum_m [H_i(m) D_i(m) + J_i(m) S_i^E(m)] + \sum_i \sum_{m'} [R_i(m') D_i(m') + T_i(m') S_i^N(m')] \quad (2)$$

where W, E, F, G, H, J, R and T are constants, Q_i, S_i^E and S_i^N are, respectively, the net charge, electrophilic superdelocalizability and nucleophilic superdelocalizability of atom i. The index m (m') refers to the contribution to the above properties of occupied (virtual) molecular orbital m (m'). Equation (2) was derived by accepting that the only important component of ΔE is the change in electronic energy. The physical meaning of these indices has been discussed elsewhere; therefore, we shall comment only on the indices appearing in the results [10, 13].

We must emphasize that only drug-related terms appear in Equations (1) and (2). This is so because, in the model employed to derive them, it is assumed that we are dealing with a family of drugs interacting with the same partner (receptor, enzyme, etc.). Then, the electronic terms of the common partner (AChE here) are constants that do not appear explicitly.

On the other hand, the derivation of Equation (1) does not involve any assumption about the way of calculating the reactivity indices appearing in it. Therefore, they can be calculated at any desired level (using semiempirical methods or *ab initio* ones with any basis set). Any method is acceptable if it gives good results in calculating reactivity indices whose variation (and not their absolute values) explains the variation of the affinity within a given drug family. For the same reason, the physical interpretation of the terms appearing in Equation (1) is independent of the quantum-chemical method used to find their numerical values.

The moment of inertia terms deserve a comment. We have proposed that they can be expressed in a first approximation as [18]:

$$\log(I_1 I_2 I_2) = \sum_t \sum_i m_{i,t} R_{i,t}^2 = \sum_t O_t \quad (3)$$

where the summation over t is over the different substituents of the molecule, $m_{i,t}$ is the mass of the ith atom belonging to the tth substituent, $R_{i,t}$ being its distance to the atom to which the substituent is attached.

This approximation allows us to transform a molecular property (i.e., $\log(I_1 I_2 I_3)$), into a sum of substituent properties. As the physical interpretation of the terms appearing in Equation (3) we propose that they represent the fraction of molecules attaining the proper orientation to interact with their partner. For this reason we shall refer to them as orientational parameters (OP).

The numerical values of the OPs are obtained as follows. The substituent atom that is attached to the skeleton is placed on the x axis of a Cartesian coordinate framework. Its distance to the point (0, 0, 0) is chosen to be equal to Pople's standard distance between it and a tetrahedral carbon atom [19]. The remaining substituent atoms are placed according to the conformation to be calculated. Pople's standard bond angles and distances are employed. The central expression in Equation (3) is applied to this set, thus obtaining the OP's numerical values. As Ref. [18] is not readily available, we present in Table I the OPs used to obtain the results. The orientational parameters can be calculated for different conformations of the substituent. The OP value for the most extended conformer

TABLE I
Standard values for the orientational parameters of some substituents (uma · Å^2)[a]

Substituent	Orientational parameter
—H	1.1975
—F	35.1394
—Cl	110.6945
—Br	299.8161
—Me	41.5361
—Et	141.1041
—*n*—Pr	366.3316 (e)
—*i*—Pr	239.5504 (e)
—*t*—Bu	338.0469
—*sec*—Bu	464.8031 (e), 338.0219 (f)
—OMe	122.4838
—OEt	328.6994 (e), 210.9740 (f)
—O—*i*—Pr	446.6210 (e), 387.7584 (f)
—O—*n*—Bu	1229.0786 (e), 773.9599 (f)
—CN	121.7507
—NO_2	206.9421
—CF_3	348.6496
—CHO	123.3573
—COEt	462.3322
—SMe	226.6843
—*SO_2Me*	454.3501

[a]From Ref. [15]. (e) and (f) mean, respectively, extended and folded.

is called extended (O^e), and the one for the least extended (more folded) conformer, folded (O^f) [18]. This immediately suggests that at working temperature we may have the case in which a substituent may adopt a variety of conformations. One way to ameliorate the OP values for this case could be through the use of a weighted sum over the OPs of the existing conformations at a given temperature.

Inserting Equations (2) and (3) into Equation (1), we get the final equation expressing the relationship between activity and electronic/conformational parameters of only the drug molecules.

Numerical values for the electronic parameters were obtained from a molecular wave function calculated within molecular orbital theory at the CNDO/2 level, using standard geometrical parameters [19]. This geometry was employed because it is assumed that a skeleton, common to all the molecules being studied, interacts with the macromolecule. In this case, the contribution of the substituents is through the modification of the skeleton's electronic properties. Our earlier work using CNDO/2 geometries has shown that this choice is a good one [10–13]. Another point to consider is whether some parts of the molecules are solvated or not. We have assumed that the insecticide enters AChE in desolvated form. Also, we took care that the numerical values of the nucleophilic superdelocalizabilities behave well [20].

The molecules selected, together with their experimental equilibrium constants,

were taken from the literature [4]. The experimental values were transformed to $A = -\log K$ (affinity constant).

Results and Discussion

The electronic parameters were calculated for a common skeleton including the aromatic ring and the —$OCONHCH_3$ moiety. A multiple regression analysis was then carried out for this skeleton to select the best equation.

None of the regression equations including all the molecules was statistically significant. Therefore, we separated them into *ortho-*, *meta-* and *para*-substituted groups. For the *ortho-* and *para*-substituted NMC we found a single equation. In the *meta*-substituted group it was not possible to do this. Therefore, we proceeded in the following way: we started with those molecules substituted with alkane fragments, adding all the molecules which improved the equation. From the remaining molecules, we selected those containing *O*-alkyl substituents, proceeding in a similar fashion. This is not necessarily the best way to do it, but as a first approach it is satisfactory

The results are the following.

1. *ortho-Substituted Phenyl-N-methylcarbamates*

The best equation is:

$$A = 3.7321 - 3.8695(\pm 0.8233)D_3(H-2) + 0.0019(\pm 0.0005)O^e_{ortho} \tag{4}$$

$$n = 14, \quad r = 0.93, \quad s = 0.23, \quad F(2, 11) = 41.49 \ (p < 0.0001)$$

where O^e_{ortho} is the extended orientational parameter for the *ortho* substituents and $D_3(H-2)$ is the orbital electronic density of Molecular Orbital (MO) (HOMO-2) at atom 3.

The analysis of variance shows that this equation is statistically significant. The results of Student's t test for the significance of the variables of Equation (4) are: $t[D_3(H-2)] = -4.70$ ($p < 0.01$), and $t[O^e_{ortho}] = 3.95$ ($p < 0.025$). The square of the internal correlation coefficient, $r^2[D_3(H-2), O^e_{ortho}]$, is 0.30. From these last data, we may appreciate that all the variables appearing in Equation (4) are significant and uncorrelated. The predicted A values using Equation (4) are presented in Table II.

The analysis of the coefficients and variables appearing in Equation (4) shows that an ideal molecule should have a low contribution of atom 3 to the electron density of the $(H-2)$ MO, and a high orientational parameter value for the *ortho* substituent. We must keep in mind that the highest value of O^e_{ortho} cannot exceed the highest one employed in the generation of Equation (4). Also, we must insist that the appearance of this orientational parameter does not suggest the existence of a pocket in AChE, but merely indicates that the extended conformation contributes to a better NMC–ChE interaction. Finally, we must remember that the appearance of only electronic parameters related to the inner MOs does not

Table II
Experimental and calculated equilibrium constants for *ortho*-substituted phenyl-*N*-methylcarbamates

Substituent	Exp. K[a]	Calc. K[b]
—H	2.520	2.486
—F	3.033	3.033
—Cl	3.597	3.650
—Br	4.167	4.270
—Me	2.609	2.883
—Et	3.029	3.208
—*n*—Pr	3.403	3.607
—*i*—Pr	3.907	3.681
—*sec*—Bu	4.288	4.172
—OMe	3.385	3.428
—OEt	3.790	3.807
—O—*i*—Pr	4.401	4.383
—CN	3.801	3.214
—NO_2	3.892	3.920

[a]From Ref. [4].
[b]With Equation (4).

indicate that the external ones do not participate in the reaction. In fact, they do not appear because the regression equation displays only those variables whose variation explains the variation of the affinity. Therefore, the parameters that remain constant throughout a series of molecules are included in the constant.

2. *meta-Substituted Phenyl-N-methylcarbamates*

The best equation found for the first group is:

$$A = 2.9507 + 99.4520(\pm 32.9906)S^{E}_{11}(H-2) + 0.0017(\pm 0.0002)O^{f}_{meta} \tag{5}$$

$$n = 8, \quad r = 0.82, \quad s = 0.20, \quad F(2,5) = 46.36 \ (p < 0.005)$$

where $S^{E}_{11}(H-2)$ and O^{f}_{meta} are, respectively, the orbital electrophilic superdelocalizability of MO (HOMO-2) at atom 11 and the orientational parameter of the folded *meta* substituents.

Other statistical parameters for Equation (5) are $t[S^{E}_{11}(H-2)] = 3.01$ ($p < 0.05$), $t[O^{f}_{meta}] = 7.08$ ($p < 0.005$), and $r^2(S^{E}_{11}(H-2), O^{f}_{meta}] = 0.17$. The experimental and predicted A values are presented in Table III.

Equation (5) indicates that the affinity of NMC for AChE increases when the electron-donor capacity of $(H-2)$ MO at atom 11 diminishes. The appearance of the folded orientational parameter instead of the extended one suggests that some of the *meta* substituents are in that conformation when they interact with AChE.

TABLE III
Experimental and calculated equilibrium constants for *meta*-substituted phenyl-*N*-methylcarbamates

Substituent	Exp. K[a]	Calc. K[b]	Calc. K[c]
—F	2.380	2.451	
—Cl	2.991	2.845	
—Br	3.225	3.337	
—NO_2	3.220	3.272	
—OEt	3.206	3.037	
—O—*i*—Pr	3.462	3.418	
—O—*n*—Bu	4.000	4.060	
—OMe	2.695	2.859	
—H	2.520		2.670
—CF_3	3.320		3.348
—Me	3.425		3.331
—Et	4.190		4.059
—*n*—Pr	4.910		4.685
—*i*—PI	5.256		5.442
—*t*—Bu	5.495		5.524
—CHO	2.733		2.623
—COEt	3.369		3.500
—CN	3.068		3.155

[a]From Ref. [4].
[b]With Equation (5).
[c]With Equation (6).

The best equation for the other *meta*-substituted NMC group is:

$$A = -25.2008 + 158.7820(\pm 9.5729)Q_1 - \\ - 18.0715(\pm 3.6369)S_7^N(L+1) + 0.0034(\pm 0.0004)O^e_{meta} \quad (6)$$

$$n = 10, \quad r = 0.99, \quad s = 0.17, \quad F(3,6) = 136.12 \ (p < 0.0005),$$

where Q_1, $S_7^N(L+1)$ and O^e_{meta} are, respectively, the net charge of atom 1, the orbital nucleophilic superdelocalizability of MO (LUMO + 1) at atom 7, and the orientational parameter for the extended *meta* substituent.

This equation has $t[S_7^N(L+1)] = -4.99$ ($p < 0.005$) and $t[O^e_{meta}] = 9.75$ ($p < 0.0005$). The squares of the internal correlation coefficients are: $r^2[Q_1, S_7^N(L+1)] = 0.002$, $r^2[Q_1, Q^e_{meta}] = 0.0001$, and $r^2[S_7^N(L+1), Q^e_{meta}] = 0.0001$. The experimental and calculated A values are presented in Table III.

The analysis of this equation shows that increased affinity is related to the existence of a positive net charge on atom 1 and to a low electron-accepting ability of atom 7. Also, the orientation parameter should be high (extended conformations seem to be preferred).

TABLE IV
Experimental and calculated equilibrium constants for *para*-substituted phenyl-*N*-methylcarbamates

Substituent	Exp. K[a]	Calc. K[b]
—H	2.520	2.972
—Cl	2.500	2.761
—Br	2.693	2.834
—Me	2.793	2.991
—Et	3.026	3.067
—*n*—Pr	3.041	3.170
—*i*—Pr	3.420	3.137
—*t*—Bu	3.155	2.886
—OMe	3.068	3.104
—OEt	3.217	3.227
—O—*n*—Bu	3.569	3.774
—SMe	3.032	2.898
—CHO	3.640	3.746
—COEt	3.027	2.982
—SO_2Me	3.360	3.088
—CN	3.695	3.168
—NO_3	3.987	3.909

[a]From Ref. [4].
[b]With Equation (7).

3. *para-Substituted Phenyl-N-methylcarbamates*

The best equation is:

$$A = 2.6157 + 3.3837(\pm 0.7082)D_7(H-2) + \\ + 16.0755(\pm 6.9106)D_{11}(H-2) + 0.0007(\pm 0.0002)O^e_{para} \quad (7)$$

$$n = 17, \quad r = 0.81, \quad s = 0.27, \quad F(3, 13) = 9.08 \ (p < 0.005),$$

where O^e_{para} is the extended orientational parameter of the *para* substituent.

Other statistical indices for Equation (7) are: $t[D_7(H-2)] = 4.78$ $(p < 0.05)$, $t[D_{11}(H-2)] = 2.33$ $(p < 0.05)$, $t[O^e_{para}] = 2.92$ $(p < 0.025)$, $r^2[D_7(H-2), D_{11}(H-2)] = 0.12$, $r^2[D_7(H-2), O^e_{para}] = 0.04$, and $r^2[D_{11}(H-2), O^e_{para}] = 0.00005$. The experimental and predicted A values are shown in Table IV.

Equation (7) shows that optimal affinity is reached when there are high contributions from atoms 7 and 11 to the (HOPMO-2) MO. The appearance of $D_{11}(H-2)$could be related to an electrostatic interaction contributing to diminish the degrees of freedom of the NMC molecule to facilitate its reaction with AChE. The orientational parameter has the same meaning as above.

From the above correlation coefficents, we may appreciate that Equations (4–7) explain, respectively, 86.5%, 67.2%, 98% and 65.6% of the variation of A. Two main factors account for these results:

1. The experimental conditions used to measure A. In general it is accepted that regression equations with an s value of about 0.20 are acceptable in the case

of biological measurements. In our case only Equation (7) does not fulfill this condition and, as expected, it has the lowest r value.

2. In several of the molecules analyzed here, the substituent has one or more rotational degrees of freedom. A more accurate calculation must include, not the extended or folded OP values, but a weighted sum including at least the main rotamers. This could be an important source of error in the case of, for example, the *O-n*-butyl substituent, where the folded OP value is 773.96 and the extended one 1227.08.

From the foregoing analysis, the following points emerge:

a. The conditions imposed by Equation (4) on *ortho*-substituted NMC are fulfilled by substituents whose electronegativity allows them to remove charge from the ring and which are small enough to avoid strong repulsive charge distribution interactions. It can be seen that the best A values correspond to this kind of substituent, such as Br and *O-i*-Pr.

b. For *meta*-substituted NMC the highest A values are for the cases of bulky and apolar substituents. In the first group of molecules, the appearance of the folded OP suggests their passage through a region demanding the highest substituent apolarity. For the other group, those bulky substituents that can increase the net charge of atom 1 seem to be the most suitable.

c. For the *para*-substituted NMC, substituents with high extended OP values, also having electron donating properties to increase charge densities of atoms 7 and 11, provide the highest affinity. Also note that the poor prediction of the A value for the CN-substituted NMC can be explained because, although this group is a good electron donor, it has a low OP value.

The integration of Equations (4–7) allow us to propose a common interaction mechanism of NMC's with AChE. In this mechanism, atoms 1 and 3 interact electrostatically with complementary sites of AChE in order to form the reversible complex. This binding is probably enhanced by an electrostatic interaction or a charge transfer from atom 11. This last suggestion is supported by the following line of thought. In the molecules studied here, the $(H-1)$ and $(H-2)$ molecular orbitals are of π nature and delocalized over the heavy atoms of the whole system. As charge transfer contributions of the $(H-2)$ molecular orbital at several atoms appear in the final equations, it can be inferred that $(H-1)$ molecular orbital also participates, at least at the level of atoms 3, 7 and 11. Nevertheless, in the case of atom 11, we do not have enough elements to distinguish whether we are dealing with a charge transfer or with an electrostatic interaction.

Topliss *et al.* have suggested that there is a risk of arriving at fortuitous correlations when too many variables are screened relative to the number of available observations [21–23]. In the case of empirical methods (as defined in the Introduction), this is perfectly possible, given their nature. For non-empirical methods, Topliss *et al.*'s statement does not hold. The reason is that the final equations of a non-empirical method are not suggested, but derived. Therefore, we are working with a system of equations that must have a solution. On the contrary, when a structure-activity relationship is stated without any formal derivation we cannot prove that a solution exists. Therefore, the use of regression analysis in empirical

and non-empirical methods is based on totally different philosophies: in the latter ones we are not searching for a solution, but finding the best one.

Another point to comment on is the generation of more than one equation for a set of apparently similar molecules. At first sight, this fact seems surprising. Nevertheless, there are no *a priori* reasons to hold that a single equation must be obtained. In fact, non-empirical models are able to display subtle differences (in this case the substituent's position) that deeply modify the conditions for the drug-receptor interaction. The influence of the substituent's position on the equilibrium constant has also been shown to hold for opiates [24].

Finally, we must emphasize the following two points:

1. Due to their formal origin, the orientational parameters are able to provide good QSAR's for a set of small molecules with substitutions at sites which must obviously affect the time required for the drug molecule to reach the proper orientation to interact with a macromolecule. The justification is as follows. It is assumed that the molecular set interacts with the receptor through a common skeleton. This common skeleton has some substituents attached to it. The whole molecular system rotates around its principal axes. When the molecule approaches the receptor site it must be properly aligned to be able to enter. In physical terms this means that the translation and rotation velocities must be modified. Due to thermal agitation there must be a limiting time for the alignment. If this time is exceeded, the molecule will continue along its path without interacting with the receptor. This is consistent with the physical meaning of the orientational parameters and the best example, apart from the work reported here, is the case of the opiates that had seemed to have no solution [24].

2. CNDO/2 shows once again that it is still a good method to calculate static reactivity indices for QSAR. The excellent results it affords when applied to other biologically active molecules [13, 24–26], its predictive ability [11, 12], and its coupling to new developments in the continuum representation of electrostatic medium effects for non-spherical systems [27, 28], makes it difficult to declare obsolete for QSAR studies.

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