

Compatibility of the Free-Wilson and Hansch Quantitative Structure-Activity Relations

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Whether or not the Free-Wilson and Hansch methods are compatible depends upon the functional relation connecting the independent variables of the two methods. This relation is often unknown.

The question of whether or not the Free-Wilson and the Hansch treatments of drug activity are consistent with each other has been discussed in the literature for the past decade. The earliest explicit treatment of the point appears to be that of Singer and Purcell¹ who, using a particular set of assumptions, examined the problem in some detail. Here we shall reexamine the question in more generality.

Consider a set of compounds and let f_k ($k = 1, 2, \dots, K$) be some function of the biological activity of the k th member. Commonly,

$$f_k = \log(1/C_k) \quad (1)$$

where C_k is the concentration of compound k required to produce some specified biological response,² but any of a great variety of functions might be used. One wishes to construct some mathematical model which will give a good approximation, \tilde{f}_k , to f_k . In the Hansch method, \tilde{f}_k is related to other physical properties of the molecule by

$$\tilde{f}_k = F(P_{1k}, P_{2k}, \dots) \quad (2)$$

where P_{1k}, P_{2k}, \dots are values of properties 1, 2, ... of compound k . The best form of the function F and the optimum choice of the P_{ik} are debatable, but to be specific let us first suppose F to be the commonly used³ quadratic function of π

$$\tilde{f}_k = a\pi_k^2 + b\pi_k + c \quad (3)$$

where π_k is the logarithm of the ratio of the octanol-water partition coefficient of compound k to that of a standard. The Free-Wilson approach⁴ is fundamentally different and does not relate biological activity to other physical properties. Instead the biological activity is assumed to be an additive function of contributions from local regions in the molecule. Again to be specific, suppose the molecules considered are all of the same basic structure and differ only at two nonequivalent local sites. Let the possible substituents at the first site be X_1, X_2, \dots, X_N and those at the other be Y_1, Y_2, \dots, Y_M . Then

$$\tilde{f}_k = \mu + \sum_{i=1}^N n_{ki}x_i + \sum_{j=1}^M m_{kj}y_j \quad (4)$$

where x_i is the contribution of the group X_i to the biological activity, n_{ki} is the number of times (0 or 1) this group appears in the k th molecule, and y_j and m_{kj} are defined analogously for substituent Y_j . The constant μ is usually described as the activity of the molecule minus its substituents, but it turns out more precisely to be the average of the experimental biological activities when eq 4 is fit to experimental data by the original Free-Wilson method or equal to the calculated activity of the hydrogen-substituted compound in the Fujita-Ban variant.⁵⁻⁷ In the original paper on the Free-Wilson method,⁴ and in many since, the variables n_{ki} and m_{kj} were not indicated explicitly. Doing so gives the somewhat cumbersome eq 4 which is, nevertheless, easier to follow through the manipulations of the least-squares method.

At this point, either, both, or neither of eq 3 and 4 might give a good prediction of biological activities. Without further information (experimental, theoretical, or postulated) there is no relation between the variable π_k in eq 3 and the variables n_{ki} and m_{kj} in eq 4, and it is impossible to say whether the two equations are consistent or not. Suppose it is assumed that π_k , like \tilde{f}_k in the Free-Wilson method, can be partitioned as a sum of additive contributions from local regions in the molecule. If these local regions are the same as those in eq 4, then

$$\pi_k = \alpha + \sum_{i=1}^N n_{ki}\pi_{xi} + \sum_{j=1}^M m_{kj}\pi_{yj} \quad (5)$$

where n_{ki} and m_{kj} are as defined in eq 4 and π_{xi} is the contribution to π of the substituent X_i and π_{yj} is that of Y_j . Equation 5 has been used by Hansch⁸ and many others and is perhaps the most common assumption connecting the variables of eq 3 and 4. Substituting eq 5 into eq 3 gives eq 6. The first three terms of eq 6 are of the same form as those of eq 4, but the three quadratic terms in eq 6 do not appear in eq 4. Hence, eq 3 and 4 are not consistent given the assumption of eq 5. Had eq 3 contained no quadratic term in π_k , then eq 3 and 4 would have been

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$$\bar{f}_k = (a\alpha^2 + b\alpha + c) + (2\alpha a + b) \sum_{i=1}^N n_{ki} \pi_{xi} + (2\alpha a + b) \sum_{j=1}^M m_{kj} \pi_{yj} + a \left(\sum_{i=1}^N n_{ki} \pi_{xi} \right)^2 + a \left(\sum_{j=1}^M m_{kj} \pi_{yj} \right)^2 + 2a \sum_{i=1}^N \sum_{j=1}^M n_{ki} m_{kj} \pi_{xi} \pi_{yj} \quad (6)$$

consistent as can be seen by setting $\alpha = 0$ in eq 6.

Franke⁹ has also considered the case in which, although the parabolic relation (3) does hold, the data actually used all lie on one wing of the parabola, which can then be approximated by a straight line. In this case the Free-Wilson method (eq 4) and the Hansch method (eq 3) are again consistent.

However, eq 5 is only one possible assumption connecting the variables of the two methods. It might be instead that π_k^2 can be partitioned as in eq 5 to give

$$\pi_k^2 = \alpha + \sum_{i=1}^N n_{ki} \pi_{xi} + \sum_{j=1}^M m_{kj} \pi_{yj} \quad (7)$$

or perhaps the combination $(a\pi_k^2 + b\pi_k + c)$ can be partitioned.

$$(a\pi_k^2 + b\pi_k + c) = \alpha + \sum_{i=1}^N n_{ki} \pi_{xi} + \sum_{j=1}^M m_{kj} \pi_{yj} \quad (8)$$

With the assumption of eq 8, the Free-Wilson method (eq 4) and the Hansch method (eq 3) are consistent but not with the assumptions of eq 7 or 5, except in the special cases mentioned above.

Without knowledge of the relation between the variables in the Hansch and Free-Wilson treatments, and this lack of knowledge would seem to be the usual case, no statement can be made about the consistency of the two. In particular, the fact that a Hansch equation with a quadratic term gives a good prediction of biological activity does not in itself imply that the Free-Wilson equation will not also give equally good predictions in the same case.

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Synthesis and Evaluation of the Male Antifertility Properties of a Series of N-Unsubstituted Sulfamates

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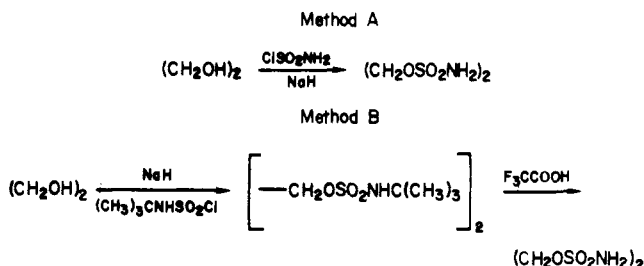
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A series of six aliphatic and one carbocyclic N-unsubstituted sulfamates have been synthesized and evaluated as potential male antifertility agents. Three of the aliphatic sulfamates, 1,2-ethanediyl sulfamate (1), 1,3-propanediyl sulfamate (2), and 1,4-butanediyl sulfamate (3), when administered orally to male rats caused a decrease in the number of pregnant females and/or implantation coupled with increased embryonic and fetal resorption. The compounds were prepared by treating the appropriate glycol salt with sulfamoyl chloride or by the cleavage of a *tert*-butylsulfamate with trifluoroacetic acid.

Chemicals that interfere with the postmeiotic transformation of spermatozoa in either the testis or epididymis can cause the production of morphologically intact but sterile spermatozoa, a state designated as "functional sterility". These spermatozoa are either unable to penetrate and fertilize an ovum or render the embryo or fetus unable to sustain development. Trimethyl phosphate,¹ various esters of methanesulfonic acid,² and 3-chloropropane-1,2-diol³ are examples of a few classes of compounds which have been shown to produce "functional sterility" in animal models. The latter compound has shown the most promise, since its antifertility action involves only spermatozoa in the epididymis and causes them to be unable to penetrate or fertilize an ovum, thus eliminating the possibility of a mutagenic effect.

This paper describes the synthesis and evaluation of a series of six aliphatic and one carbocyclic N-unsubstituted sulfamates as potential male antifertility agents, hopefully

Scheme I



acting by causing "functional sterility". The sulfamate group was chosen because of its chemical similarity to the methanesulfonic acid esters and its occurrence in the antibiotic nucleocidin.⁴

Of the sulfamates reported in this paper, compounds 1-3 (Table I) exhibited "functional sterility", with the most potency exhibited by compounds 1 and 3. The compounds appear to act by altering the normal function of spermatids

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