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QSAR: RATIONAL APPROACHES TO THE DESIGN OF BIOACTIVE COMPOUNDS

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QSAR: Rational Approaches to the Design of Bioactive Compounds

DRUG DESIGN H-BONDING SCALE

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SUMMARY

The QSARs revelation really have a need to take H-bond into account. To be usefull in QSAR the H-bonding ability of chemicals should be represented quantitatively. In this work an approach to empirical computation of the H-bond thermodynamic values is based on multiplicativity principle by means of factors ($E_i(E_j)$ and $C_i(C_j)$), which present the quantitative measure of contribution from each compound to enthalpy(ΔH) and free energy(ΔG) of H-complexes. The applicability of this principle was verified on large set of experimental data on thermodynamics of H-complexes. The set of novel H-bonding descriptors was derived from donor(acceptor) factors. These descriptors were used in programs CLARAS and DNESTR. The QSAR models obtained using the factors were good enough.

INTRODUCTION.

A successful modeling of new specific biologically active compounds is conceptually based on molecular recognition. Thermodynamic criterions of molecular recognition in conditions of competitive complex formation have been formulated in (ref.1). Recognizer (biologically active compound) A_o, located in medium that contains N kinds of effectors (right effector is B_o and wrong ones are $B_1, B_2, .., B_{N-1}$) in arbitrary concentrations, can bind up with each of them. Accepting wrong recognition (e.g. A_oB_1, $A_oB_2, .., A_oB_{N-1}$ complex formation) probability P_f as the measure of specificity, we can perform it, in simplest way of complex formation with stoihometry 1:1, as follows:

$$P_f = \frac{\sum_{i=1}^{N-1} [A_oB_i]}{[A_oB_o] + \sum_{i=1}^{N-1} [A_oB_i] + [A_o]} = \frac{\sum_{i=1}^{N-1} K_{oi}[B_i]}{K_{oo} + \sum_{i=1}^{N-1} K_{oi}[B_i] + 1} \qquad (1)$$

where

$$[A_oB_i]/[A_o][B_i] = K_{oi} = \exp(-\Delta G_{oi}/RT),\ i = 0,1,..,N-1 \qquad (2)$$

Consequently, with increasing of differences in binding constants between B_o and B_i with A_o(e.g. Gibbs energies of complex formation ΔG_{oo} and ΔG_{oi}), the recognition reliability increases, too.

The reasons above are evidently show that thermodynamic description of molecular interactions should be a subject of attentive consideration in any kind of QSAR investigations. In biological systems the overwhelming majority

of intermolecular processes are possible due to H-bonds(ref.2), that is why the quantitative estimation of a H-bond thermodynamic parameters is of great necessity for modeling of structure-activity correlations.

The knowledge about both enthalpy (ΔH) and free energy (ΔG), connected by the well-known relationship:

$$\Delta G = \Delta H - T\Delta S, \quad (3)$$

are of equal importance for QSAR because ΔH is a measure of strength of bond between two molecules, and ΔG is that of binding probability. It is evidently seen from eqn.(3), that maximal yield of complexes formed will take place if ΔS is positive and ΔH is negative. One can distinguish three main approaches to determination of a H-bond thermodynamic functions: (i) experimental, (ii) calculative, (iii) correlative.

The first approach is quite reliable, but unfortunately one can't experimentally measure enthalpy or enthropy of complex formation between hypothetical molecules. The second one, based on traditional quantum chemical calculations for enthalpy estimation and on Monte-Carlo studies or molecular dynamics for that of enthropy could do it, but time and computer resources requirements are too large by now. The third approach is based on using of various sets of parameters (H-bond scales) which allows to calculate thermodynamic functions by means of analytical relationships accepting this parameters. The next kinds of formulae were used in different sources: additive(ref.3), multiplicative(ref.4) and additive-multiplicative(ref.5).

In present work some results of investigations that were being carried out during fifteen year period are presented(refs.6-8). These investigations were directed to forming of unified H-bonding scale for drug design. Also examples are shown of using this scale when modeling QSARs. The legality of appliance of this approach to various classes of chemical compounds was thoroughly verified by means of reliable experimental procedures.

RESULTS AND DISCUSSION.

In present work we set a problem to construct a system of empirical parameters to make possible a quick calculation of ΔH and ΔG using multiplicative approach. This kind of relationships was chosen after Iogansen proposed to use the products of acid or base functions for calculation of an enthalpy of the H- bond formation in 1971(ref.4). The multiplicative approach is based on constancy and mutual independence of functions mentioned above and may be written as follows:

$$\Delta H_{ij} = \Delta H_{11} P_i E_j, \quad (4)$$

where ΔH_{11} = 22.2 kJ/mole is an enthalpy of complex formation between standard pair(phenol(P_1)-diethylether(E_1) in CCl_4), P_i and E_j are acid and base functions which we shall note, below, as protonodonor(accepter) factors(P_1 is

equal to 1 and E_i is equal to -1), also we shell note protonodonor factors as E_i rather than P_i. The thermodynamic data were collected from works that were published in last 15 years. This data set contains values of thermodynamic functions on reactions involving compounds with various donor(accepter) groups. It includes near 1000 reactions in CCl_4 between about 300 protonoaccepters and protonodonors. The protonoaccepters were simple and complex ethers, aldehydes and ketones, sulphoxides and phosphoryl compounds, pyridines and its derivatives, alkylamines and nitryles. The protonodonors were presented by phenols, alcoholes, alyphatic and aromatic acids. Compounds and reactions were chosen in order to make all factors calculated to be statistically significant. The enthalpy factors were calculated using equation (6) and equation:

$$\Delta G_{ij} = \Delta G_{11} C_i C_j \qquad (5)$$

was used to calculate free energy factors, here ΔG_{11} is free energy of complex formation between phenol and diethylether having $C_{PhOH}=1$ and $C_{Et_2O}=-1$. Also, it was set that E_i or C_i are greater than 0 and E_j or C_j are less than 0. The values of some $E_{i(j)}$ and $C_{i(j)}$ calculated are presented in table 1. The correspondence of experimentally measured values of ΔH to those calculated using enthalpy factors is looks as follows:

$$\Delta H_{calc.} = -0.38(\pm 0.61) + 0.99(\pm 0.03)\Delta H_{exp.} \qquad (6)$$
N=703, R=0.942, SD=2.8, F=5517

The values of C_i and C_j still more statistically significant than $E_{i(j)}$, so the same relationship for ΔG is:

$$\Delta G_{calc.} = -0.32(\pm 0.23) + 1.03(\pm 0.02)\Delta G_{exp} \qquad (7)$$
N=703, R=0.962, SD=1.6, F=8780

The drug design H-bonding scale, descibed in this work, is unified one and it does systematize, we believe, another scales, that were obtained on dif-

TABLE 1

Protonodonor(accepter) factors of compounds having various functional groups(an active site is marked by asterisk).

Protonodonors			Protonoaccepters		
Compound	E_i	C_i	Compound	E_j	C_j
$CCl_3-CH_2-OH^*$	-0.84	0.76	$(C_6H_5)_3PO^*$	1.44	3.01
$CBr_3-CH_2-OH^*$	-0.81	0.71	$(C_6H_5O)_3PO^*$	1.00	1.66
$CF_3-CH_2-OH^*$	-0.96	1.00	$[(CH_3)_2N]_3PO^*$	1.49	3.44
$CH_3-CH_2-OH^*$	-0.59	0.45	CH_3-CN^*	1.01	0.88
$CH_2Cl-COOH^*$	-1.37	1.60	$CH-CN^*$	1.16	0.73
$CHCl_2-COOH^*$	-1.43	2.14	CCl_3-CN^*	0.33	0.41
CCl_3-COOH^*	-1.59	2.78	$CH_3-C(O^*)-O-CH_3$	0.78	0.77
$C_4H_9-NH^*-NO_2$	-0.86	0.94	$CH_3-C(O^*)-C_4H_9$	1.13	1.24
$C_3H_7-NH^*-NO_2$	-0.85	0.93	$CH_3-C(O^*)NH-C_4H_9$	1.43	2.15
$CH_3-NH^*-NO_2$	-0.92	1.00	$CH_3-C(O^*)-O-C_2H_5$	0.69	0.31

ferent classes of compounds or in different solvents or using different basic reactions. For example, β-parameters of phosphorylic compounds, presented in(ref.10), could be transfered to E_j by means of correlation established:

$$E_i = 0.26(\pm0.03) + 1.01(\pm0.04)\beta \quad (8)$$
$$n = 49,\ R = 0.991,\ SD = 0.02,\ F = 2619$$

The H-bonding scale for drug design described in (ref.11) and based on values of stability constsants ($lg\ K_{a(b)}$) of H-complex formation in C_2HCl_3 related to our presentation as:

$$lg\ K_{a(b)} = -0.42(\pm0.13) + 1.64(\pm0.10)C_i(C_j) \quad (9)$$
$$n = 39,\ R = 0.984,\ SD = 0.37,\ F = 1096$$

Therefore, the H-bonding ability of these compounds can be compared with that of different chemical classes' represetatitives.

To take H-complex formation into consideration in our QSAR reseaches the set of descriptors was derived from factors: $E_i^{max}(E_j^{max})$ - the factor of the most active site, ΣE-the sum of all factors in molecule, ΣE/Molecular weight, ΣE/Molecular volume etc. This descriptors set was used(together with large set of topological and physico-chemical descriptors) in our QSAR program complex CLARAS(ref.9) and DNESTR. The sufficient role of these descriptors in SARs for cholinesterase inhibitors, insecticide carbamates, antiinflamatory phenols and carbon acids, etc. was established.

Examples:

fungicide activity of phenols

$$lg\ 1/C_0 = 2.41 + 1.67C_i^{max} \quad (10)$$
$$n=8,\quad R=0.96,\quad SD=0.34,\quad F=61$$

β-adrenergic activity of substitute phenethylamines

$$lg\ K_0 = 5.10+3.8E_i^{max}-0.11\Sigma E_i/Chi_1 \quad (11)$$
$$n=15,\quad R=0.92,\quad SD=0.42,\quad F=81$$

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