ELECTROSTATICS IN COMPUTER-AIDED DRUG DESIGN

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Abstract: Hydrogen bonds and charge-charge interactions, determined by molecular electrostatics, play essential role in biopolymer-ligand associations. Accordingly, electrostatics is crucial in the qualitative and quantitative characterisation of the binding of drugs to their target molecules. In the following, we will give an account on the role of molecular electrostatics in a drug design, laying emphasis on our own work. We will survey the most important computation methods of molecular electrostatic potentials, then outline basic aspects of molecular recognition: steric, electrostatic and hydrophobic complementarity. On the basis of the complementarity, we will also define molecular similarity and discuss various applications of these concepts to the treatment of protein-ligand interactions and a rational drug design. Special attention will be paid to a receptor mapping and to a comparative molecular field analysis, with some our recent applications. A further important point will be the molecular electrostatic field (potential gradient) as a hydrophobicity measure. We will argue that the hydrophobic complementarity and similarity can be treated on the basis of matching regions of the interacting molecules that are characterised by a similar magnitude of the electrostatic field. The concept of the electrostatic complementarity will be extended to enzyme-substrate interactions, providing a firm basis for the quantitative estimation of catalytic rate enhancement.

Keywords: electrostatics, drug design, molecular electrostatic potential, molecular electrostatic field, similarity, pharmacophore, CoMFA method, protein-ligand interaction

1. Introduction

Modern drug design is based on two different, but complementary, approaches [1-4]. One is the combinatorial chemistry applying brute force or rationally designed methods for the synthesis and screening of a large number of related molecules. The other is the structure-based drug development where the three-dimensional structure of the biological target and its complexes formed with various ligands are determined, yielding sufficient information for the design and/or optimisation of appropriate lead molecules. Analysis of the energetics of drug-ligand interactions is a prerequisite for successful predictions. Thus, the role of electrostatics, determining most aspects of target-drug interactions, cannot be overseen. For example, molecular similarity, a concept quite often used in analysis of combinatorial libraries, may be partially characterised in terms of electrostatics. In this way, electrostatics may play a role in the rational design of such libraries.

In the following, we give a survey on the role of electrostatics in the structure-based drug design. First we discuss methodology, then molecular complementarity and similarity will be treated, while in the last section we present some applications coming from our laboratories.

2. Methodology

Non-covalent interactions between drugs and macromolecules are mainly governed by the free energy of association between the partners, and the leading term of the interaction energy is electrostatics. If we do not consider hydrophobic effects, that should be treated quite differently, we may apply classical methods for free energy estimates, therefore time-consuming quantum mechanical calculations become superfluous or should be restricted to some small systems of basic importance. The electrostatic contribution to the total interaction energy can be calculated either in terms of atomic multipoles or the molecular electrostatic potential (MEP) and its gradient the molecular electrostatic field (MEF) that can be exactly derived from the total wave function. While the multipole expansion of the energy yields numbers, that may surprisingly well approximate the exact value, the MEP provides a pictorial representation of the interaction pattern showing attractive and repulsive regions around a molecular system. Since, in this paper we put emphasis mainly on the MEP, we mention here only the most important methods that are widely used for its calculation (for a recent review see ref. 5).

For small drug molecules with less than 30 non-hydrogen atoms the best method for calculating the MEP and MEF is quantum mechanics. Molecular orbital and density functional methods are now available that provide the above electrostatic properties with a quite high accuracy. For the larger systems, like oligopeptides, DNA mimics or some natural products monopole and multipole approximations (e.g. potential-derived charges) are amended, while the protein electrostatic potentials are best calculated by the solution of the linearized Poisson-Boltzmann equation [6]. In this method a biomolecule is immersed in a continuous medium modelling the solvent, which effect is mimicked by an appropriate dielectric model. The equation is based on the supposition that the distribution of mobile ions around the solute follows the Boltzmann distribution law. Its advantage over other methods is that it is applicable to arbitrary geometries and non-uniform dielectrics. A numerical solution is done by the computer code, DelPhi, which is a highly successful software with hundreds of applications to a wide variety of proteins and other biomolecules [7].

3. Complementarity and Similarity

Protein-ligand complementarity is determined by the three major factors, steric, electrostatic and hydrophobic [8, 9]. The most important is the steric fit, but host and guest must match also electrostatically, which means that the net interaction between their various regions should be attractive. The electrostatic complementarity is optimal, if the positively and negatively charged or inversely

polarised groups of the interacting molecules get close to each other, and it can be analysed in terms of the MEP that sheds light on e.g. crystal-field [10] or point-mutation effects [11]. Nakamura and co-workers defined a quantitative measure of electrostatic complementarity on the basis of MEP products [12]

$$P = \Sigma P_i / \mathrm{N} \tag{1}$$

with

$$P_i = \mathrm{sign}\,(V_i^H \times V_i^G)\,(V_i^H \times V_i^G)^{1/2} \tag{2}$$

where V_i^P and V_i^A denote the molecular electrostatic potential at point i emerging from the host and guest, respectively. We slightly modified this expression by summing for a set of N points, {i}, on the van der Waals surface of the guest including only regions around potentially hydrogen-bonding atoms (e.g. N, O or and bound acid H) [13]. A more negative value of P refers to a better complementarity and corresponds to a larger value of the electrostatic interaction energy between associating partners.

The hydrophobic complementarity is related to hydration and dehydration of the ligand upon complex formation and can be formulated as the matching between regions of the host and guest that are of similar polarity, i.e. have the same ability to bind water molecules [11, 14, 15]. This property is appropriately characterised by the MEF, thus hydrophobic aspects of complementarity may be discussed in terms of matching of the MEF patterns produced by host and guest. Those regions of the associated molecules, that are characterised by a small MEF, i.e. small hydration energy (hydrophobic regions), tend to associate in order to minimise unfavourable entropy effects by removing water from the contact surface. On the other hand, hydrophilic regions with a large MEF also tend to associate providing that the contacting charges are opposite in sign. We formulated the *similis simili gaudet* principle [11] which means that the regions with similar MEF values tend to associate stronger than dissimilar ones. The principle could be applied with success to explain the specificity of point mutants of trypsin and subtilisin [16].

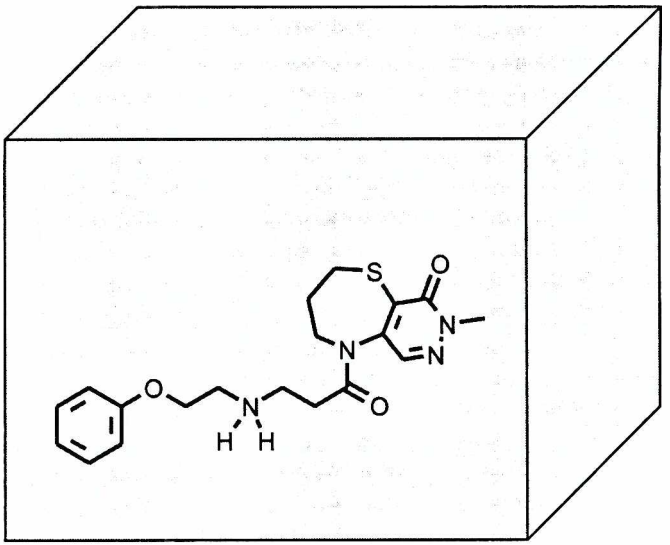
The concept of molecular complementarity can be well used for a drug (ligand) design if the 3D structure of the receptor is known [1, 2]. However, such structures are not always available, even if their number increases fast. In such cases the concept of molecular similarity, closely related to complementarity, may be well used. Molecular similarity may be defined in terms of the congruency of molecular shapes as well as the MEP and MEF. There are known qualitative and quantitative definitions, here we refer only to the comprehensive survey by Mezey [17].

There are two important methods of drug design that are based on molecular similarity [18–22]. Molecular modelling makes use of various computational methods to define the *pharmacophore*, i.e. the 3D arrangements of functional groups and stereoelectronic features (e.g. hydrogen-bonding donor and acceptor sites, hydrophobic centres) that are essential for ligand binding to the target biopolymer, or to carry out the so-called *receptor mapping*. The crucial step of

these approaches is to identify the common features and bioactive 3D arrangements in a series of compounds. Taking into account that these latter are not necessarily identical to the minimum energy structure, the first step in finding biologically active geometries is mapping of the conformational space. The pharmacophore is then obtained by comparing various, often intuitively selected, alignments of low-energy conformers of a series of active and inactive ligands by computer graphics. The pharmacophore provides a basis on which a plausible explanation for the differences of binding affinities can be provided for each molecule.

There are automatic mapping procedures available which define hydrogen-bonding site points and centres, then use a clique detection method along with a distance comparison for the assignment and characterisation of similarity. The DISCO [21] and APEX-3D [22] programs are most popular but other methods have also proven to be efficient alternatives [18-20]. For the DISCO analysis a set of conformers (at most one hundred) is supplied for each compound. In order to generate a representative conformer set, various methods are used. Conformer generators select various energy minima of a molecule by perturbing torsion angles randomly. Some variants change the geometry of those atoms only that determine site points and other binding centres. The conformer set, generated as above, will be used to identify possible pharmacophores via superposition of the various conformers with a reference structure that can be defined by the user or the program itself. The DISCO may usually present a number of pharmacophores of which it is often difficult to select the best one. Good selection criteria are offered by some model scores (e.g. r.m.s. fit, union or reference volume) and examination of fits of molecular parts other than identified by the pharmacophore. The predictive power of a pharmacophore can be validated by investigating the inactive and active compounds not included in the original model building process.

The Comparative molecular field analysis (CoMFA) [23] is another important method exploiting the similarity concept in a drug design. It is assumed that a suitable sampling of the steric extension and electrostatic field around a ligand molecule provides all the information necessary for describing its biological activity. The steric and electrostatic contributions to the total interaction energy of the ligand with a probe are calculated via the Coulomb and Lennard-Jones approximations at regularly spaced grid points of a 3D lattice surrounding it (cf. Figure 1). In the QSAR data table the dependent variable is the biological activity that is a function of various structural parameters. The Partial Least Squares (PLS) method is applied in order to derive linear equations from this highly under-determined matrix, and a cross-validation ensures the statistical significance of the final equation. An appealing feature of the PLS method is, that the criterion of acceptance is the improvement of the ability to predict the biological activity. The resulted quantitative-structure activity equation may be visualised as a contour map highlighting the sensitivity of the biological activity to steric and electrostatic effects. These maps are useful tools for understanding the relationship between



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compounds	*pIC_{50}*	*S001*	...	*S999*	*E001*	...	*E999*
GYKI16287	7.71						
GYKI16476	6.79						
GYKI16477	7.43						
...							

↓

PLS

↓

pIC50 = a * S001...+ m * S999 + n * E001 +...+ z * E999 + y

↓

Contour maps

Figure 1. *Illustration of the CoMFA process.*

structure and activity as well as designing new compounds. The greatest problem with CoMFA is the definition of a superposition rule, because it defines the orientation of each ligand relative to all others [24, 25].

It should be mentioned that in the standard CoMFA applications to interactions between receptor and ligand are interpreted only by steric and electrostatic complementarity, the hydrophobic aspect is not directly considered. As we discussed above, the MEF is an appropriate descriptor for hydrophobic interactions, however, several types of a molecular lipophilicity potential can be defined [26-29] and they may also be used as a determinant in CoMFA [30].

4. Applications

In the following, we present some recent applications of the above concepts to the problems of a ligand binding and a drug design. We focus on examples of the electrostatic and hydrophobic complementarity, as well as similarity. The concept of electrostatic complementarity could be well exploited in case of the analysis of binding of the transition-state complex by the enzyme active sites [13]. Electrostatic

Table 1. *Electrostatic complementarity values (P), calculated relative stabilization energies, $\Delta\Delta G_{calc}$, and measured activation energies, $\Delta\Delta G_{meas} = -2.303RT \log (k_{cat}/K_M)$, of the transition-state complex for some serine proteases with the succinyl-Ala-Ala-Pro-Phe-p-nitro-anilide substrate.*

	P	$\Delta\Delta G_{calc}$	$\Delta\Delta G_{meas}$
Subtilisin *Carlsberg*	-6.9	-102.6	-36.5
α-chymotrypsin	-5.1	-71.9	-34.2
Subtilisin *NOVO*	-3.8	-62.1	-31.6
β-trypsin	-1.2	-40.7	-26.7
α-lytic protease	8.0	9.3	0.3

potentials at the enzyme active sites with the (– + –) charge distribution were calculated using the linearized Poisson-Boltzmann equation. It was found, for all cases studied (serine proteases, lipase, acetylcholinesterase, lysozyme, D-xylose isomerase), that the protein and substrate electrostatic potential patterns on the van

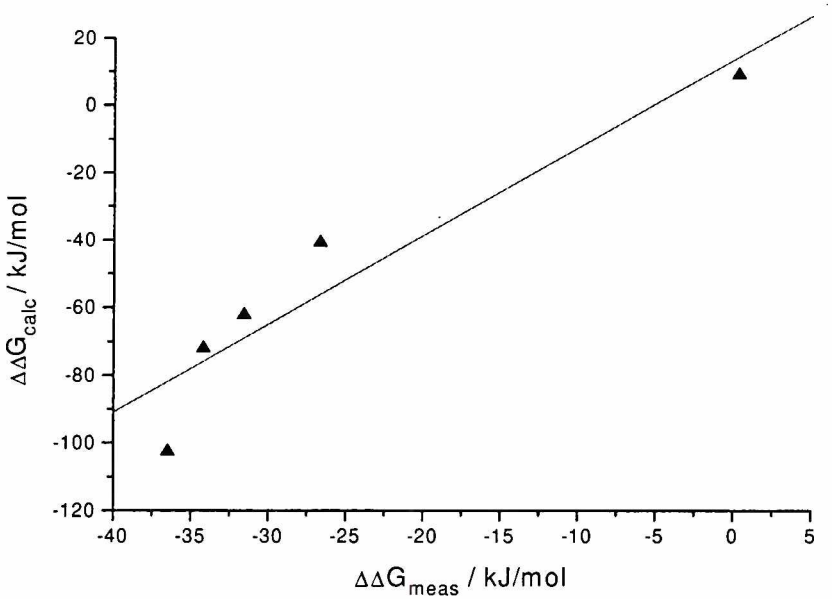

Figure 2. *Correlation of calculated electrostatic and experimental binding energies of the succinyl-Ala-Ala-Pro-Phe-p-nitroanilide substrate to serine proteases.*

der Waals envelope of both molecules complement each other. Enzyme activities, as characterized by log k_{cat}/k_M for the identical substrates (succinyl-Ala-Ala-Pro-Phe-*p*-nitro-anilide) of α-chymotrypsin, β-trypsin, α-lytic protease, subtilisin *Novo* and subtilisin *Carlsberg*, respectively, correlate well with the calculated electrostatic interaction energies between the protein environment and the active site, if the

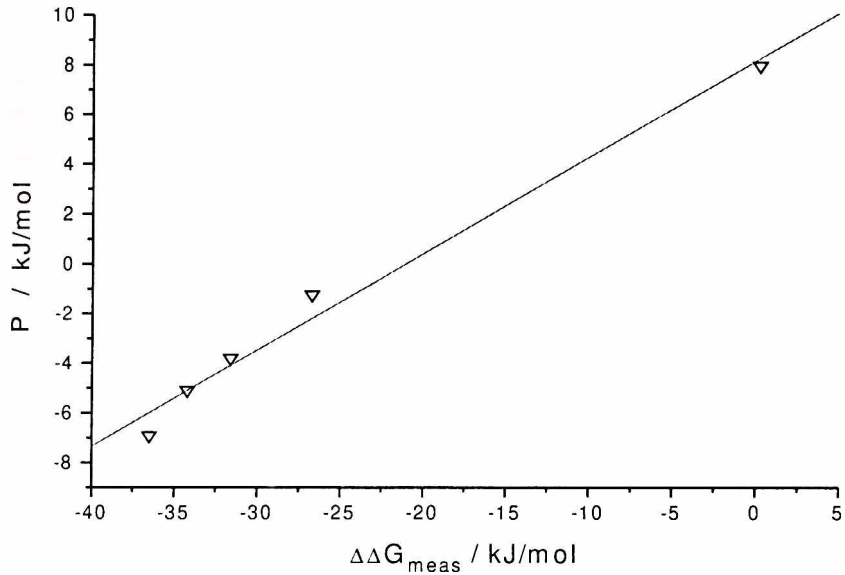

Figure 3. *Correlation of calculated electrostatic complementarity values and experimental binding energies of the succinyl-Ala-Ala-Pro-Phe-p-nitroanilide substrate to serine proteases.*

geometry of the protein-ligand complex was appropriately optimised (cf. Table 1 and Figure 2). For the same enzymes it was found that the electrostatic complementary values between the active site and protein environment, as defined in eqs. (1-2), correlate with electrostatic interaction energies, as well as activities (cf. Figure 3). Though, absolute magnitudes of the calculated stabilisation energies are overestimated by the factor of about 2, the overall trends are well reproduced. This indicates that the variation of the protein environment around the bound substrate essentially influences the catalytic rate via its electrostatic effect.

As we discussed above, a simple way to characterise the hydrophobic complementarity is to consider the MEF on the van der Waals envelope of the interacting partners. This idea has beed applied by us to00002 derive some quantitative structure-activity relationships. We proposed the following equation for the *P* Hansch hydrophobicity indices of small molecules [15b]:

$$\log P = -0.190F - 0.010S_{ua} + 0.200 + 0.0014S_pF + 2.77 \qquad (3)$$

r = 0.9614 n = 18 F = 63.0 s = 1.83

Here S, S_{ua} and S_p refer to the total molecular surface, its unsaturated apolar and polar components, respectively. Though the predictive power is not very good, eq. (3) provides a rationale, why F could be well applied in two, otherwise very different structure-activity relationships: (i) for the prediction of activities of psychotomimetic phenylalkyl-amines [31] and (ii) the adsorption abilities of organic compounds on metal oxide surfaces [32]. A similar relation to eq. (3) could be derived for the Wolfenden hydrophobicity scale of amino-acid residues [15a]:

$$HP(W) = -0.756F - 0.251S_p + 3.25S_p/(S_{sa}+S_{ua}) + 22.0 \quad (4)$$

r = 0.9614 n = 18 F = 63.0 s = 1.83

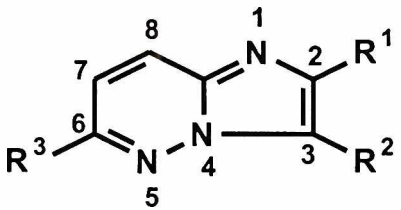

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Figure 4. *General formula of imidazo[1, 2-b]pyridazines possessing affinities in benzodiazepine receptors.*

In order to illustrate the applications of a receptor mapping and the CoMFA methods we present some own examples. In recent years Barlin et al. synthesized a number of imidazo[1, 2-*b*]pyridazines of type 1 (Figure 4), and some structurally relating ring systems, which showed from moderate to high binding affinities to benzodiazepine receptors. In the molecular modelling studies [33, 34], where conformational analyses were carried out by molecular mechanics, and molecular properties were calculated by semiempirical methods, we succeeded in identifying binding sites for these compounds, and in developing pharmacophores for compounds of the modest and high affinities. Perhaps one of the most interesting aspects of these studies was the interpretation of strikingly different activities of 6-anilino, 6-phenetylamino derivatives *vs.* 6-benzylamino derivatives in the 3-methoxy series, and providing an explanation for the conflicting role of the 6-benzyloxy substituent in the 3-methoxy *vs.* 3-acylamino series. Analysing the geometries of these compounds, it could be pointed out, that the phenyl ring of the 6-benzylamino and the 3-benzoylamino substituents in the two series, respectively, may represent an additional binding site for the receptor by a *face-to-face* or a *edge-to-face* stacking. Thereby a five-point pharmacophore could be proposed for the most active compounds. Our CoMFA model was also consistent with this proposal [35].

Following the similar strategy, we were also able to define pharmacophores for the antiarrhythmic and anxiolytic compounds. In a study for the class III antiarrhythmic agents, nine, mainly structurally unrelated compounds with cardiac repolarization lengthening effects and I_{Kr} blocking properties, were included [36]. We divided these compounds into two subsets containing the highly and less potent agents. Then, the DISCO analyses of conformers generated by the Multisearch method for both sets were performed. As possible solutions, 53 models were obtained for the first set. On the basis of model scores, relative energies of conformations included in the model, and fits of complete molecules, one five-point, *lege artis* validated final model pharmacophore, could be selected. For the second set, a four-point pharmacophore could only be identified, what may account for the reduced activity of this set of compounds.

The next example illustrates the successful combination of the DISCO and CoMFA procedures. In an effort to develop the QSAR model for serotonine-1A receptors, we identified common structural features present in anxiolytic pyridazinothiazepines and pyridazinooxazepines (a typical representative of which is shown in Figure 4) by the DISCO analysis [37, 38]. The pharmacophore thus obtained served as a starting point for the CoMFA. It is noteworthy, that hierarchical cluster analysis for selecting a test set of compounds, the sample-distance partial least squares (SAMPLS) procedure for statistical analysis, and region-focusing for weighting the CoMFA lattice points, were used in this study. Results of these analyses indicated the significance of the model, small standard errors, and statistically insignificant probability of a spurious correlation. Furthermore, as illustrated by a predictive set of compounds, this model may be generally expected to provide a good performance for structurally related compounds.

Finally, as a useful alternative of the direct and indirect approaches, a homology modelling with a subsequent ligand docking (see ref. 39 as a recent review on the method) could be mentioned. Accordingly, the primary amino acid sequence of the target protein is used, together with an experimentally determined 3D structure of a close protein analogue as a template, to build up the target. This strategy is illustrated by our study on interaction of thienocyloheptapyridazines with the human m1-receptors [40]. The receptor-ligand interaction energies were also analysed. Interaction energies of the receptor-ligand optimized complexes were calculated by using the formula $IE = E_{complex} - E_{receptor} - E_{ligand}$, and indices of H-bonding and electrostatic energy components (as specific interactions), together with the van der Waals contribution (as non-specific interactions) with respect to the total interaction energy, were also determined. Interestingly, it was found that binding of agonists and partial agonists consists mainly of specific interactions, whereas antagonists bind to the m1-receptors by the van der Waals interactions. Thereby, such strategy could not only be useful for *de novo* design, but also in this way qualitative differences in the antagonist and agonist binding modes could be translated into quantitative models.

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