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# INTERACTION OF ANTIBODIES WITH AROMATIC LIGANDS: THE ROLE OF π-STACKING

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Antibodies are responsible for antigen recognition in vertebrate organisms. Practically any molecule can be bound by antibodies. In this work structures of 73 complexes of antibodies with small antigens were taken from PDB database and compared. The main epitope of studied ligands was an aromatic ring. Antibodies bound it with a deep cavity, lying between complementary determining regions (CDR) H3 and L3 and formed by aromatic residues. In most cases the aromatic ring of ligand was placed parallel to one or two aromatic sidechains of binding site at 3.5-4 Angstrom distance. This disposition of aromatic rings is a sign of the presence of π-stacking. It was found that small ligands with aromatics area percentage $> 36\%$ predominantly form π-stacking interaction with antibodies. Most often this interaction was observed for residues in positions H33, H95, L32 and L93.

*Keywords*: Antibody; small aromatic antigens; π-stacking.

## 1. Introduction

Antibodies represent a class of protein molecules which are responsible for antigen recognition in vertebrate organisms. The basis of antibody domain structure is β-framework bearing surface loops. Antigen binding region consists of six hypervariable loops (or complementary determining regions (CDR)), which provide the

diversity of binding surface. It is important that backbone structure of five out of six loops are determined by the set of "canonical classes".[1] CDR H3 has a more complicated structure. The gene of CDR H3 is derived by recombination of original V, D and J genes[2] followed by maturation. CDR H3 shows significant variability in length and sequence compared to other CDRs. Nevertheless, we can divide CDR H3 into two parts: a relatively predictable "torso" (determined by V and J genes) and a shorter "apex", which is less studied.[3] Owing to the conservative structure of an antibody, the modeling of antibodies is relatively simple compared to other proteins. This makes antibodies a very promising platform for studying ligand-protein interaction generally.

The thermodynamics of antigen-ligand interaction includes enthalpic and entropic factors. Enthalpy of interaction appears as a result of contributions of hydrogen bonds, ion pairing and Van-der-Waals interactions.[5] Entropy is estimated as a sum of two changes: negative conformational and translational entropy of the forming complex and positive "solvent" entropy rising from water recoordination from buried hydrophobic surfaces. The latter factor is evidently more important in the case of small ligands. It was shown that for ligands of big or medium size antibody binding site approves any spatial conformation, but for most small ligands the dominant form of a binding site is a cavity or a hole.[6,7] It should be noted, that the "induced fit" binding mechanism seems unsuitable in this case. Owing to the ligand size the influence of a ligand on an antibody conformation is virtually impossible. As a result the cavities preexist on the antibody binding site surface. These small cavities always bear aromatic amino acid residues on their inner surface and we can conclude that if a small ligand contains an aromatic ring, it only serves as an epitope for the antibody. Thus, it is involved into $\pi$-stacking interaction. Sometimes,

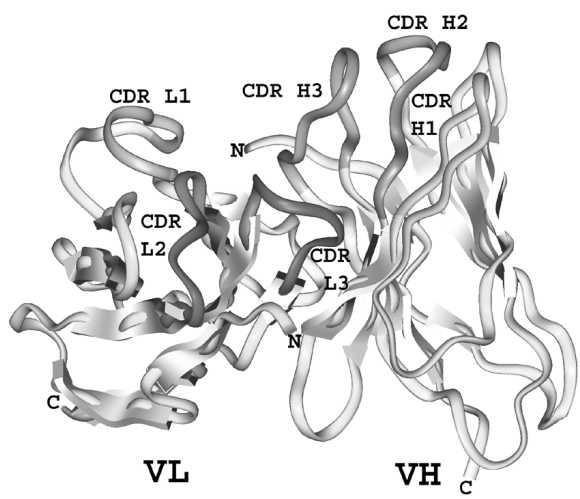



Fig. 1. General view of an antibody binding site.[4]

formation of hydrogen bonds or ion pairs with small ligands is possible, but that is unlikely.

$\pi$-stacking is a special type of electron dispersion effect appearing between $\pi$-electron systems.[8] For small aromatic rings (less than ca. 10 atoms) this interaction is very weak, and can be approximated as trivial Van-der-Waals force. In aqueous solutions "entropic" factor dominates the "enthalpic" one. The formation of $\pi$-stacking shields hydrophobic planes of aromatic rings from water molecules. As noted above, it leads to water liberation and increase of "solvent" entropy in the whole system. Thus, we can use the term "$\pi$-stacking" as a geometrical descriptor of interaction mode in aromatics.[8]

Due to widespread distribution of aromatics in nature $\pi$-stacking is a common interaction for biological macromolecules, but is usually used in the description of nucleic acids structure only. It is well-known that this interaction often contributes to the formation of the hydrophobic core of proteins.[9] Some aromatic cofactors bind with enzymes via $\pi$-stacking, as will be shown below. Less well-known is the fact that it is the main driving force for small aromatic molecules to bind with antibodies. We plan to demonstrate this thesis. Taking this factor into account can improve automatic modeling methods.

## 2. Methods

### 2.1. *Sources of information and programs*

We used three-dimensional structures of antigen-antibody complexes obtained from Protein Data Bank (http://www.rcsb.org/). SwissPDBViewer 3.7 (http://www.expasy.org/spdbv) and PyMOL 0.99 ( http://www.pymol.org) were used for structure visualization. Insight II software (http://accelrys.com/) was applied for homology modeling, structure optimization and docking. Sequences of antibodies were marked in accordance with Kabat.[10]

### 2.2. *E2/B5 antibody: structure modeling, biochemical characterization.*

Modeling methods and docking procedure were described before.[11] Dissociation constants were calculated from enzyme-linked immunoassay data which were obtained in accordance with the published method.[12]

## 3. Results and Discussion

### 3.1. *Task setup*

To reveal the role of $\pi$-stacking in antibody-antigen complexes it was planned to search the database for the presence of this type of interaction. Obviously the target antigen should be relatively small aromatic compound. The limit of maximum 50 heavy atoms was chosen because larger structures have a too small aromatic part

for substantial contribution to binding via stacking. Then the selected structures were analyzed to find out the presence of $\pi$-stacking. In our analysis only parallel stacking cases were considered. Cases with partial intersection of electron clouds (i) were hardly detectable; (ii) had too little influence on binding. Then the factors which correlated with stacking were analyzed. Namely, we studied the dependence of number of stacking cases on ligand size, surface percentage of aromatic part of ligand, antibody structure and methods of antibody elaboration.

### 3.2. *$\pi$-stacking consideration*

The full scan of PDB database for small aromatic antigens in antibody-antigen complexes was performed. The files containing antigen structures with less than 50 heavy atoms and including aromatic part were selected for consideration. 114 of 880 browsed structures were selected for further study. When for the same antibody more than one crystal structure with the same antigen was found, the most representative of them was selected. Thus, structures of 73 antibody-antigen complexes were chosen.

It was revealed that complexes with varied ligands contained the same stacking interactions. The common feature of these complexes was the presence of two (or three in sandwich-type structures) parallel aromatic rings, one of which belonged to antigen and the other to antibody aromatic aminoacid residue(s) (Fig. 2). The distance between antigen aromatic ring and aromatic sidechain of antibodies was less than four Angstrom. It is known that in organic crystallography the T-forms of stacking were observed,[9] but in the antibody-antigen complex structures we have

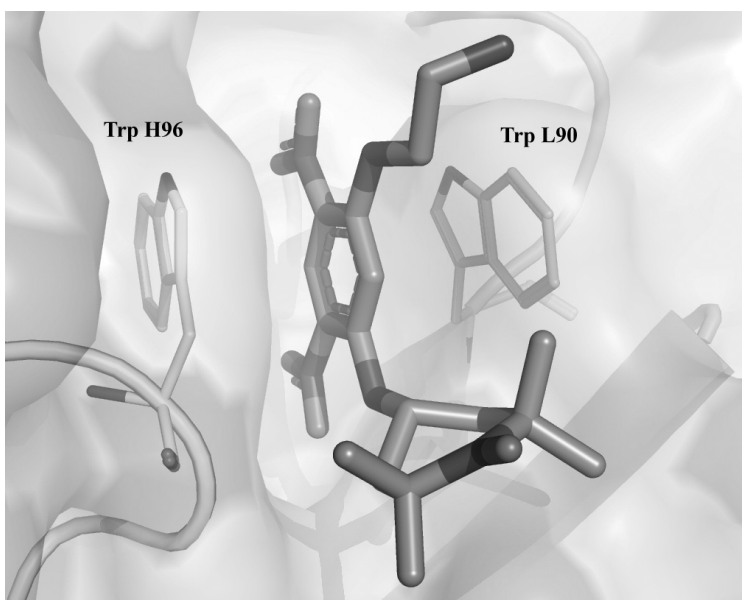



Fig. 2. Sandwich-type $\pi$-stacking between antibody and small aromatic ligand (pdb code 1baf).

Table 1. Antibody-antigen complexes which form π-stacking, CDRs and residues which involve interaction.

| PDB | Antibody name | Stacked residues | CDR |
|---|---|---|---|
| 1baf | AN02 | Trp H96, Trp L90 | H3, L3 |
| 1etz | NC10.14 | Tyr H100F, Trp L93 | H3, L3 |
| 2bjm | SPE7 | Tyr H97, Trp L93 | H3, L3 |
| 1cbv | BV04-01 | Trp H100A, Tyr L37 | H3,L1 |
| 2fl5 | – | Tyr H100A, Phe H58, Tyr H33 | H3, H2, H1 |
| 1ct8 | 7C8 | Tyr H95, Trp H50 | H3, H2 |
| 2g2r | 11G10 | Tyr H95, Tyr H33 | H3, H1 |
| 1fl3 | 19G2 | Trp H103 | H3 |
| 1ub5 | 19G2 | Trp H103 | H3 |
| 3cfb | 40-50 | Trp H103 | H3 |
| 1ibg | 40-50 | Phe H95 | H3 |
| 1d6v | AZ-28 | His H96 | H3 |
| 1kel | 28B4 | Trp H95 | H3 |
| 1hyx | 6D9 | His H97 | H3 |
| 1lo0 | 9D9 | Trp H100A | H3 |
| 1yej | D2.3 | Trp H95 | H3 |
| 1yed | D2.4 | Trp H95 | H3 |
| 1i8m | – | Tyr H100A | H3 |
| 1a4k | – | Trp H50 | H2 |
| 1c1e | 1E9 | Trp H50 | H2 |
| 1jgu | 1D4 | His H58 | H2 |
| 4fab | 4-4-20 | Trp H33, Tyr L37 | H1, L1 |
| 1aj7 | 47G7 | His H35 | H1 |
| 1keg | 64M-2 | Trp H33 | H1 |
| 1q72 | M82G2 | Trp H33 | H1 |
| 2uud | NQ10-1.12 | Tyr H33 | H1 |
| 2cju | NQ16-113.8 | Tyr H33 | H1 |
| 1kno | CNJ206 | His H35 | H1 |
| 2a9n | – | Trp L109 | L3 |
| 43ca | 43C9 | His L91 | L3 |
| 1a6v | B1-8 | Trp L93 | L3 |
| 2cgr | NC6.8 | Tyr L101 | L3 |
| 1yuh | 88C6/12 | Trp L93 | L3 |
| 1y0l | 34E4 | Trp L91 | L3 |
| 1n7m | 7G12 | Tyr L91 | L3 |
| 1oay | SPE-7 | Trp L93 | L3 |
| 1oar | SPE-7 | Trp L93 | L3 |
| 1oau | SPE-7 | Trp L93 His L97 | L3 |
| 1i3u | VHH LAMA | Tyr L62 | L2 |
| 1x9q | 4M5.3 | Tyr L32 | L1 |
| 1mrd | JEL 103 | Tyr L32 | L1 |
| 1mj7 | MS5-393 | Tyr L32 | L1 |
| 1mjj | MS6-12 | Tyr L32 | L1 |
| 1mh5 | MS6-164 | Tyr L32 | L1 |
| 1fl6 | 28B4 | Tyr L32 | L1 |
| 25c8 | 5C8 | His L34 | L1 |

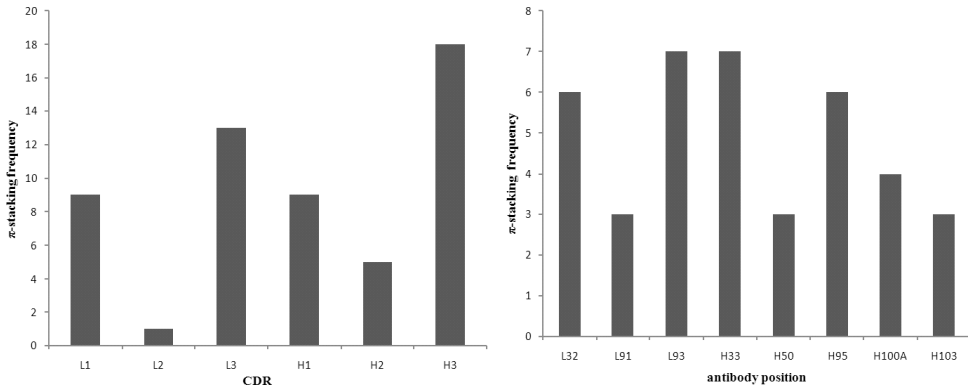



Fig. 3. CDR H3 dominating in $\pi$-stacking distribution. The residues forming the $\pi$-stacking in 3 or more cases over the database.

not found them. Obviously, for T-form case the tight fit between the cavity and the ligand is too hard to realize.

In Table 1, it is shown that 46 out of 73 structures revealed $\pi$-stacking between antigen and antibody. The distribution of $\pi$-stacking cases over CDRs demonstrated that half of them belong to abovementioned CDR H3. The main amino acid positions which were involved in $\pi$-stacking are presented in Fig. 3. The amino acids in the H33, H95, L32 and L93 positions displayed the highest frequency of interaction. It should be mentioned here that tryptophan and tyrosine were the main aromatic residues which formed $\pi$-stacking (see Fig. 4).

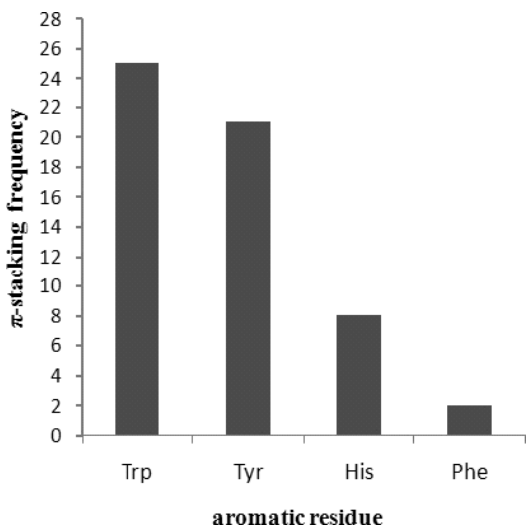



Fig. 4. Tryptophan and tyrosine are the main aromatic residues involved into $\pi$-stacking.

Table 2. Antibody-antigen complexes which do not form $\pi$-stacking.

| PDB | Antibody name | Surface percentage of aromatic part area | Comment |
|---|---|---|---|
| 1cf8 | 19A4 | 16, 44 | abzyme |
| 2bmk | 15A9 | 18, 26 | abzyme |
| 1a0q | 29G11 | 25, 08 | abzyme |
| 1eap | 17E8 | 25, 48 | abzyme |
| 1gaf | 48G7 | 26, 73 | abzyme |
| 2ajv | 7A1 | 28, 78 | abzyme |
| 1f3d | 4B2 | 35, 34 | abzyme |
| 1c5c | 21D8 | 36, 58 | abzyme |
| 1a3l | 13G5 | 48 | abzyme |
| 1ncw | 4C6 | 65, 08 | abzyme |
| 1nc2 | 2D12.5 | 12, 64 | metallocomplex |
| 1ind | CHA255 | 15, 59 | metallocomplex |
| 1igj | MAB61.1.3 | 12, 8 | small aromatic part |
| 2bfv | FV4155 | 15, 2 | small aromatic part |
| 2ddq | R310 | 15, 63 | small aromatic part |
| 2jb5 | MOR03268 | 17, 14 | small aromatic part |
| 1jnh | 10G6D6 | 20, 38 | small aromatic part |
| 1c12 | M02/05/01 | 20, 95 | small aromatic part |
| 1dl7 | M3C65 | 25, 53 | small aromatic part |
| 1jgl | 57-2 | 26, 3 | small aromatic part |
| 1jnn | 17E12E5 | 26, 77 | small aromatic part |
| 1a8j | – | 27, 85 | small aromatic part |
| 1i7z | GNC92H2 | 28, 22 | small aromatic part |
| 1q0y | 9B1 | 31, 49 | small aromatic part |
| 2pcp | 6B5 | 33, 25 | small aromatic part |
| 3cfd | EP2-25C10 | 49, 8 | non-anti-stilbene antibody |
| 2c1p | ENA11His | 67, 43 | anti-finrozole enantioselective antibody |

Table 3. $\pi$-stacking abundance for different subclasses of antibody-antigen complexes.

| | $\pi$-stacking | no $\pi$-stacking |
|---|---|---|
| area $>$ 36% | 23 | 2 |
| area $\leq$ 36% | 12 | 15 |
| abzymes | 11 | 10 |

The remaining structures (Table 2) did not involve the considered interaction despite the presence of an aromatic ring in the antigen. These structures were successfully divided into two types (Table 3):

(1) The antigens with a small percentage of aromatics area that often was combined with low accessibility of aromatic plane due to steric hindrances. Antigens referred to this group are the carcass antigens (like morphine) and metallocomplex antigens (like ferrocene). We have revealed that when the aromatic area

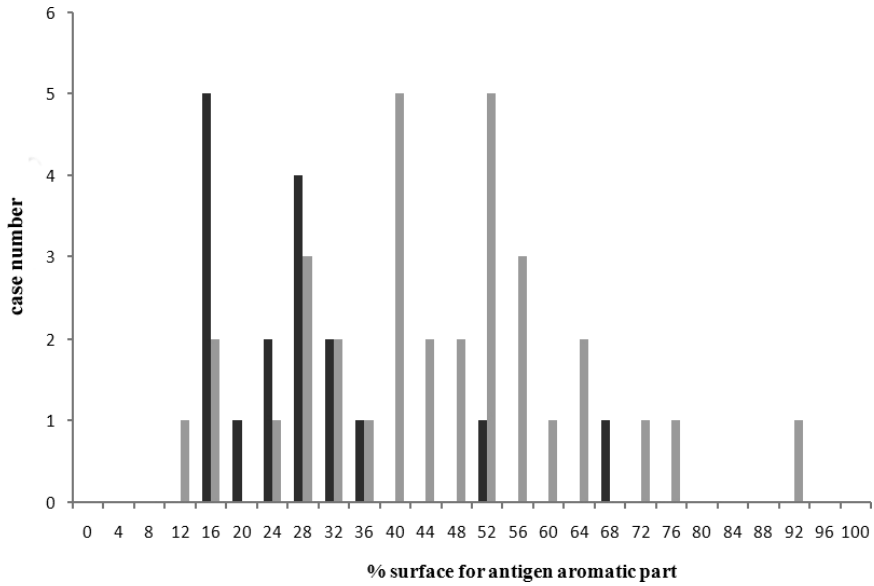


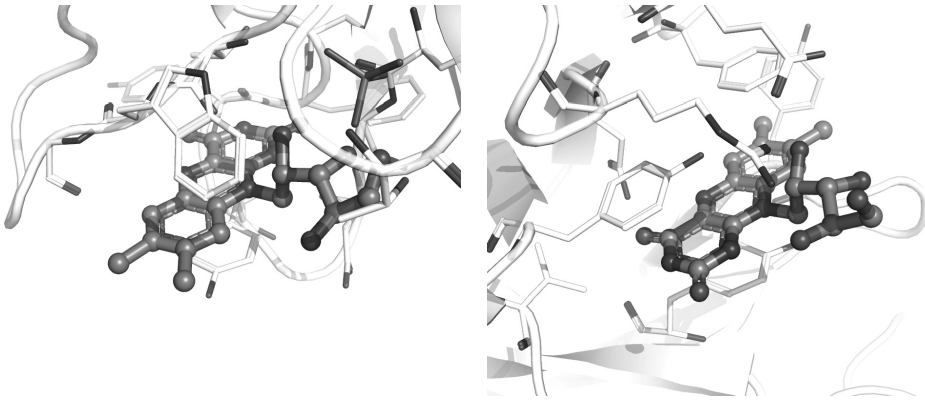

Fig. 5. The dependence of $\pi$-stacking interaction on the aromatics area percentage. Black and grey columns correspond to absence or presence of $\pi$-stacking, respectively.

is less than 36%, it leads to the decrease of the number of cases with stacking (Fig. 5). At the same time, most ligands with an aromatic area $> 36\%$ demonstrated $\pi$-stacking interaction.

(2) The structures of abzymes, which are antibodies that have catalytic activity. These antibodies are selected or elaborated as hydrolysis enzymes mainly. Aromatic rings in these reactions most often remain outside the reaction centers. Therefore, the principles of generation of such antibodies made their function independent of the absence (or presence) of $\pi$-stacking. We have not found any correlation between the properties of abzyme aromatic ligand and $\pi$-stacking presence.

The two exceptions to these rules (see Table 2) should be discussed separately. On the one hand, the antibody EP2-25C10 (PDB code 3cfd) formed complex with stilbene but was elaborated to another hapten, which resulted in the absence of the considered interaction. On the other hand, the antibody ENA11His is derived to enantioselectively bind with finrozole. Like the abzyme case, the main epitope of this antibody was the stereocenter near the aromatic ring.

It should be noted that the described principles work only for relatively small antigens. If the antigen is too large (for example, peptides that consist of six or more amino acids), it is capable of creating additional bonds with antibodies. Relatively weak $\pi$-stacking interaction was not observed in most cases of these large ligands.



(a) (b)

Fig. 6. Riboflavine in complex with apoflavodoxin (PDB code 1bu5) (a) and with antibody (PDB code 2fl5) (b).

Incidentally we have found $\pi$-stacking interaction for complexes of some studied ligands with enzymes. For instance, riboflavin revealed $\pi$-stacking with protein sidechains in complexes with an antibody and an enzyme, but the structures of complexes were significantly different (see Fig. 6). For apoflavodoxin-riboflavin complex the $\pi$-stacking interaction was formed by Tyr98 residue only. At the same time the antibody bound riboflavin by three-residue sandwich-type $\pi$-stacking interaction (with Phe H58, Tyr H33 and Tyr H100a).

### 3.3. *E2/B5 model structure examination*

The described theory can be illustrated on the basis of our recent modeling work. It was devoted to the consideration of anti-2,4-dichlorophenoxyacetic acid (2,4-D) antibodies.[11] The best studied of them, E2/B5, is a monoclonal antibody elaborated to anti-pesticide immunoassay.[13] Its model structure was derived from its sequence[14] by homology modeling. The initial structure was modeled on the basis of two matrix structures. The first matrix was used for modeling of antibody $\beta$-framework and five out of six CDRs (2rsc PDB code). The second was applied to CDR H3 modeling (1cgs PDB code). The initial structure was subjected to energy minimization in vacuum and the cycle of energy minimizations and molecular dynamics in water. The CDR-H3 "torso"-extended conformation was revealed and discussed.[4] 2,4-D docking procedure was performed with the resulting structure (Fig. 7).

The aromatics area percentage value for 2,4-D was 47%. The consideration discussed above gave us a sign of $\pi$-stacking presence in this case. Indeed, the cavity was found on the binding site surface. The cavity was tightly fitted to 2,4-D molecule size. It had a diameter of about five Angstrom and depth of up to nine Angstrom. The aromatic kernel of 2,4-D interacted with the tyrosine H95 ring.

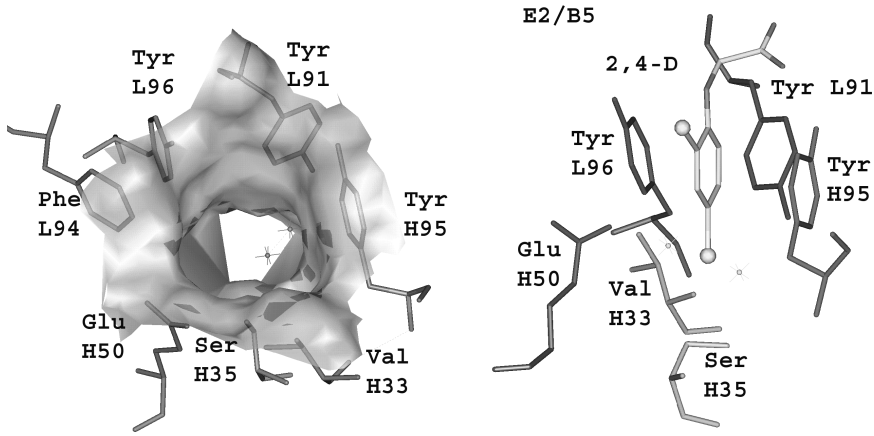



Fig. 7. Surface of the binding site cavity for E2/B5 antibody and view of model structure of 2,4-D complex with E2/B5 antibody.[7]

Aromatic residues of another hollow wall shielded the ligand kernel from water. It was shown that 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) molecule entered to the cavity incompletely, and the hydrophobic ring left exposed to solvent. This fact explained the poor binding of 2,4,5-T and its bulky analogs with anti-2,4-D antibodies.[13,14]

"Strange" disposition of a negatively charged glutamic acid residue at the cavity entrance (GluH50) can be observed. At the same time, 2,4-D was also negatively charged at neutral pH, characteristic for binding conditions. Due to this fact, from the electrostatics point of view, 2,4-D binding is unfavorable.

This contradiction could be explained by the fact that the mice immunization was performed with a conjugate of hapten with thyroglobuline[13] on the stage of antibodies generation. Hence, any conjugate of 2,4-D should be bound to this antibody better than the free pesticide. We have demonstrated this for the E2/B5 antibody by dissociation constant measuring by the Friguet ELISA method[15] modified by Bobrovnik[12] (Table 4). Obviously, the conjugate of 2,4-D with fluorescein (2,4-D-NHF) bound with the antibody more strongly than 2,4-D. This experimental data were in good correlation with the earlier published theoretical calculations.[11]

Qualitatively the fact of preferable conjugate binding in comparison with free hapten was well known, but in our case we were capable of understanding the

Table 4. Dissociation constants for fluorescein labeled (2,4-D-NHF) and free 2,4-D.

| Antigen | Dissociation constant |
|---|---|
| 2,4-D-NHF | $4(\pm 0.3)*10^{-10}$M |
| 2,4-D | $6(\pm 0.3)*10^{-8}$M |

nature of this effect. As a result, we explained on the structure model basis the improvement of competitive immunoassay sensitivity, when using any 2,4-D analog conjugates instead of 2,4-D. This was demonstrated by PFIA[16] and displacement immunoassay[17] for 2,4-D with the same monoclonal antibody set.

## 4. Conclusions

As a result, we have found that if the antigen is a small aromatic compound with an aromatic area percentage $> 36\%$ and a studied antibody is not derived for catalytic purposes, it would create a complex involving $\pi$-stacking interaction. It is necessary to take this into account during antigen–antibody complex modeling, and also during modeling of interactions of any proteins with small antigens of this type.

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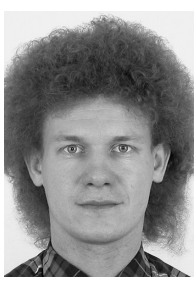

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