Three-Dimensional Structure of an Antigen-Antibody Complex at 2.8 Å Resolution

A. G. Amit, R. A. Mariuzza, S. E. V. Phillips, R. J. Poljak

The 2.8 Å resolution three-dimensional structure of a complex between an antigen (lysozyme) and the Fab fragment from a monoclonal antibody against lysozyme has been determined and refined by x-ray crystallographic techniques. No conformational changes can be observed in the tertiary structure of lysozyme compared with that determined in native crystalline forms. The quaternary structure of Fab is that of an extended conformation. The antibody combining site is a rather flat surface with protuberances and depressions formed by its amino acid side chains. The antigen-antibody interface is tightly packed, with 16 lysozyme and 17 antibody residues making close contacts. The antigen contacting residues belong to two stretches of the lysozyme polypeptide chain: residues 18 to 27 and 116 to 129. All the complementarity-determining regions and two residues outside hypervariable positions of the antibody make contact with the antigen. Most of these contacts (10 residues out of 17) are made by the heavy chain, and in particular by its third complementarity-determining region. Antigen variability and antibody specificity and affinity are discussed on the basis of the determined structure.

THE BINDING OF FOREIGN ANTIGENS TO COMPLEMENTARY structures on the surface of B and T lymphocytes represents the initial step in the sequence of events leading to activation of the immune system. The receptor molecule on the surface of B lymphocytes responsible for antigen recognition is membrane immunoglobulin. A mature B cell produces and inserts into its plasma membrane only limited amounts of a single kind of immuno-globulin. Contact with antigen results in the expansion of B cell clones specific for that antigen and in their differentiation into plasma cells capable of producing and secreting large amounts of antibody of the same specificity (monoclonal antibody).

Antibody molecules of the immunoglobulin G (IgG) class, the most abundant in normal serum, are composed of two identical light (L) and two identical heavy (H) polypeptide chains. The amino terminal regions of the H and L chains, termed V_H and V_L, are each about 110 amino acids long and have variable (and homologous) amino acid sequences. The constant (C) half of the L chain, C_L, and the constant regions C_H1, C_H2, and C_H3 of the H chain, each about 100 amino acids long, have homologous sequences that belong to one of a few classes (κ and λ for L chains; μ, δ, γ, ϵ, and α for H chains). The V_H and V_L regions each contain three hypervariable or complementarity-determining regions (CDR1, CDR2, and CDR3) responsible for antigen recognition. These are flanked by less variable (FR1, FR2, FR3, and FR4) "framework" regions (1).

Present understanding of the three-dimensional structure of antibody combining sites is based on x-ray diffraction studies of myeloma immunoglobulins as reviewed (2). These have shown that the conformation of combining sites is determined by the amino acid sequences, unique to each different antibody, of the CDR's. The structures of two complexes of antigen-binding fragments (Fab) of myeloma immunoglobulins with small ligands have also been determined (3, 4). Although these studies resulted in useful models for ligand-antibody interactions, they are insufficient to establish unequivocally the precise size and shape of antibody combining sites, the nature and extent of antigen-antibody interactions, and the occurrence of possible conformational changes (if any) in the antibody after antigen binding. In addition, the precise structure of antigenic determinants on protein molecules remains to be determined (5). Equally important are questions concerning the nature of possible conformational changes in the complexed antigen and the effect of single amino acid substitutions on antigenic specificity and antigen recognition by the antibody.

We have recently determined the three-dimensional structure of an antigen-antibody complex, one between lysozyme and the Fab fragment of a monoclonal antibody to hen egg white lysozyme, at 6 Å resolution (6). We have since extended the resolution of the x-ray structure determination to 2.8 Å, and now present a complete description of antigen-antibody interactions in the complex.

Structure determination. The production of hybrid cell lines secreting murine monoclonal antibody to hen egg white lysozyme, and the purification, crystallization (7), and 6 Å resolution crystal structure determination (6) of the complex between Fab D1.3 and lysozyme have been described. Crystals grown from solutions containing 15 to 20 percent polyethylene glycol 8000 at pH 6.0 are monoclinic, space group $P2_1$, with $a = 55.6$, $b = 143.4$, $c = 49.1$ Å, $\beta = 120.5°$, and one molecule of complex per asymmetric unit.

Three heavy atom isomorphous derivatives were prepared with $(NH_4)_2PtCl_4$, $K_3F_5UO_2$, and p-hydroxymercuribenzenesulfonate. X-ray intensities were measured to 2.8 Å resolution with the use of a four-circle automatic diffractometer. Heavy atom sites were refined in alternate cycles of phasing and refinement (8); isomorphous phases, including anomalous scattering contributions (9), were calculated. The mean figure of merit (10) to 2.8 Å resolution was 0.47 for 15592 reflections. The electron density map calculated from these data was not readily interpretable, presumably because of lack of isomorphism of the heavy atom derivatives affecting phase determination at high resolution. The phases were further refined by a density modification technique (11) with a molecular envelope traced from the Fab-lysozyme model determined at 6 Å resolution (6). The resulting phases depend only on the observed data and the overall shape and position of the complex, but are independent of the detailed conformation of the previous model (6). The resulting

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Fig. 1. Stereo diagram of the Cα skeleton of the complex. Fab is shown (upper right) with the heavy and light chains with thick and thin bonds, respectively. The lysozyme active site is the cleft containing the label HEL. Antibody-antigen interactions are most numerous between lysozyme and the heavy chain CDR loops.
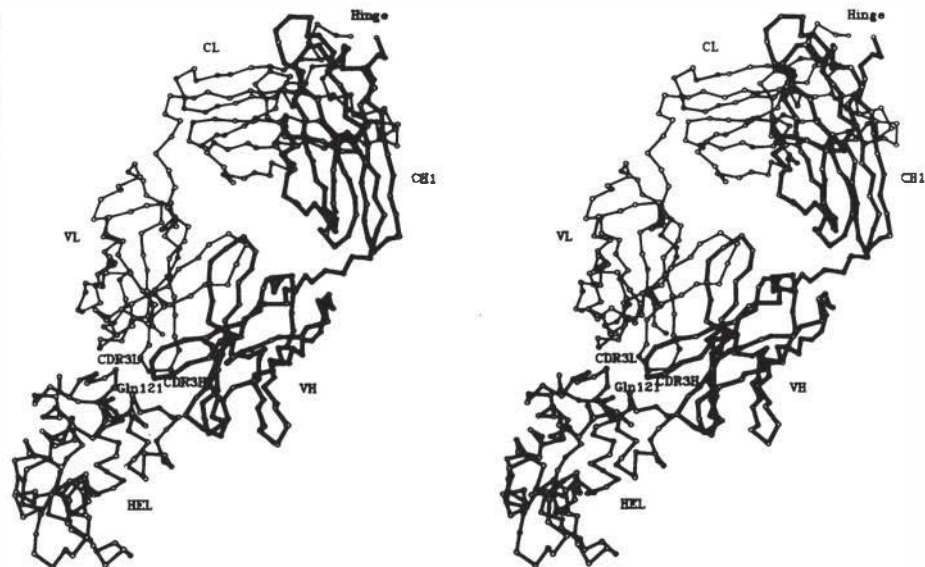
electron density map was much improved, and an atomic model was fitted to it on an Evans and Sutherland PS300 interactive graphics system with the use of the program FRODO (12). The amino acid sequence of Fab D1.3 was derived from the corresponding light and heavy chain complementary DNA (cDNA) sequences (13). Of the 562 amino acid residues in the complex, 24 of those in the constant regions could not be located in the initial map. The atomic coordinates were submitted to alternate cycles of restrained crystallographic least-squares refinement (14) and model building. The model was checked in the later stages of refinement by sequentially omitting segments of the polypeptide chain (up to 20 percent of the total) and rebuilding them in maps phased from the remainder of the structure in combination with isomorphous replacement data (15). All residues have now been located, and the current crystallographic R factor is 0.28 for all data in the 20 to 2.8 Å resolution range. ($R = \Sigma \mid |Fo| - |Fc| \mid / \Sigma |Fo|$, where Fo, Fc are the observed and calculated structure factors of x-ray reflections.) No attempt was made to locate solvent molecules. Two isotropic temperature factors were used for each residue, one for the main chain atoms, and another for the side chain atoms. Stereochemical restraints were adjusted to give a standard deviation in C–C bonds of ±0.03 Å. No restraints were applied between residues across the antibody-antigen interface. Atomic coordinates will be deposited at Brookhaven Protein Data Bank after higher resolution and crystallographic refinement.

Conformation of the complexed antigen and of the Fab. The overall structure of the complex at 2.8 Å resolution (Fig. 1) confirms the results of the 6 Å resolution study (6). The assignment of the H and L polypeptide chains of Fab is unchanged. The closely packed β sheets are seen in Fab as are the helical and β-sheet structures surrounding the active site in lysozyme. The Fab appears in an almost fully extended conformation, with a definite separation between the variable (V) and constant (C) domains. With the exception of this difference in quaternary structure, Fab D1.3 compares closely to other known Fab's (4, 16), except in the CDR loops. Predicted structures for D1.3 (17) based on other Fab's also agree well with the determined structure in the framework β-sheet regions and in some, but not all, of the CDR loops. The relative disposition of the variable subunits of the H chain (V_H) and of the L chain (V_L), is unaltered, indicating no change in quaternary structure in the V domain resulting from antigen binding. Since the crystal structure of the unliganded Fab D1.3 has not been determined, detailed changes in antibody conformation remain to be verified. However, the similarity with other Fab structures suggests

that possible conformational changes would be small. This observation is in agreement with that made by nuclear magnetic resonance (NMR) on the unliganded and hapten-liganded (dinitrophenol) mouse myeloma protein MOPC315 (18).

A least-squares fit of Cα atoms of lysozyme in the complex and native lysozyme refined at 1.6 Å in its tetragonal crystal form (19) gives a root-mean-square (rms) deviation of 0.64 Å between the two (see Fig. 2). Since the error in atomic positions in the complex can be estimated (20) to be approximately 0.6 Å, the difference is not significant. Furthermore, the largest changes (up to 1.6 Å) occur in regions remote from antibody contacts. Similar comparisons of native tetragonal lysozyme with other crystal forms gave rms deviations of 0.88 Å with triclinic lysozyme refined from x-ray and neutron diffraction data (21) and 0.46 Å for orthorhombic lysozyme determined at physiological temperature (22). Some differences in side chain conformation are observed between tetragonal and complexed lysozyme, but close examination with computer graphics revealed these to be similar to differences observed between different crystal structures of native lysozyme. Thus, complex formation with antibody D1.3 produces no more distortion of the structure of lysozyme than does crystallization.

The antigen-antibody interface. The interface between antigen and antibody extends over a large area with maximum dimensions of about 30 by 20 Å (Figs. 3 and 4). The antibody combining site appears as an irregular, rather flat surface with protuberances and depressions formed by the amino acid side chains of the CDR's of V_H and V_L. In addition, there is a small cleft between the third CDR's of V_H and V_L, corresponding to the binding site characterized in hapten-antibody complexes (3, 4). The cleft accepts the side chain Gln 121 of lysozyme although this is not the center of the antigen-antibody interface (Fig. 3).

The lysozyme antigenic determinants recognized by D1.3 are made up of two stretches of polypeptide chain, comprising residues 18 to 27 and 116 to 129, distant in the amino acid sequence but adjacent on the protein surface. All six CDR's interact with the antigen and in all, 16 antigen residues make close contacts with 17 antibody residues (Tables 1 and 2). Two antibody contacting residues, V_L Tyr 49 and V_H Thr 30, are just outside segments commonly defined as CDR's [sequence numbers are as in Kabat *et al.* (1) except for V_H CDR3; see Tables 2 and 3]. V_H Thr 30 is a constant or nearly constant residue in mouse H chain subgroups I and II, as is V_L Tyr 49 in mouse kappa chains. While the interaction of V_L Tyr 49 with antigen is relatively weak (one van der Waals
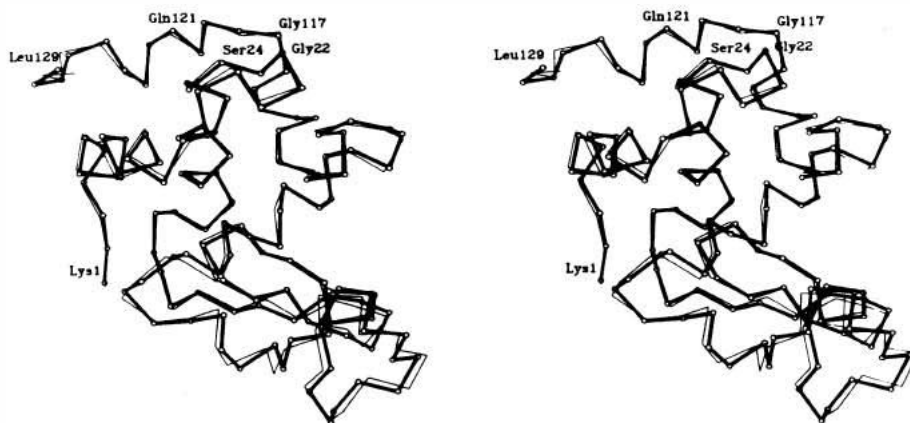
Fig. 2. The Cα skeleton of lysozyme in the complex (thick trace) superimposed by least squares on that of native lysozyme in the tetragonal crystal form (thin trace). The interface to Fab is at the top, and no significant conformation change is apparent in this region. Greater differences, although still not significant at this resolution, occur at the bottom of the molecule.

contact between its aromatic side chain and Cα of Gly 22 of lysozyme), there is a strong hydrogen bond between the hydroxyl group of V_H Thr 30 and the carbonyl oxygen of Lys 116 of lysozyme. This specific interaction involving an invariant antibody residue demonstrates that the functional distinction between "framework" (FR) and CDR residues, although largely maintained, is not absolute. The interacting surfaces are complementary, with protruding side chains of one lying in depressions of the other (Fig. 3) in common with other known protein-protein interactions (23). There are many van der Waals interactions interspersed with hydrogen bonds. This is most striking for the side chain of Gln 121, which penetrates deeply into the Fab, surrounded by three aromatic side chains, V_L Tyr 32 and Trp 92 and V_H Tyr 101 (Figs. 3, 4, and 5). Its amide nitrogen forms a strong, buried hydrogen bond to the main chain carbonyl oxygen of V_L Phe 91 (Fig. 5 and Table 3). The adjacent V_H Tyr 101 extends to the surface of lysozyme, its terminal hydroxyl group forming hydrogen bonds to the main chain nitrogens of Val 120 and Gln 121, and to Oδ1 of Asp 119. Many hydrogen bonds occur between the side chains of the antigen and the main polypeptide chain of the antibody, and vice versa (Table 3). Hydrogen bonds between main polypeptide chain atoms, similar to those in β-sheet structures, occur between Lys 116 of lysozyme and V_H Gly 31, and between Gly 117 and V_H Gly 53, where the lack of side chains allows close approach. There are many side chain–side chain close interactions forming, together with the ones

described above, a tightly packed interface which mostly excludes solvent.

Although the antigen-antibody interface involves all six CDR's of the Fab, there are more interactions with V_H than with V_L CDR's, and with V_H CDR3 in particular (Tables 1 to 3). The geometrical

Fig. 3. Space filling representation of Fab D1.3 and lysozyme. (A) Antigen-antibody complex structure as determined in this work. The antibody H chain is shown in blue, the L chain in yellow, lysozyme in green, and Gln 121 in red. (B) The Fab and lysozyme models have been pulled apart to indicate protuberances and depressions of each fit in complementary surface features of the other. Compare with (A) above. At the top of the interface, protruding V_L residues His 30 and Tyr 32 fit into a depression in lysozyme, between residues Ile 124 and Leu 129 (see also Table 1). Below the Gln 121, in red, a protuberance of lysozyme consisting of residues around Thr 118 fits into a surface depression formed by V_H residues of CDR1 and CDR2 (V_H Trp 52 can be seen at the bottom of this depression). (C) End-on views of the antibody combining site (left) and the antigenic markers of lysozyme recognized by antibody D1.3, formed from (B) above, by rotating each of the molecules approximately 90° about a vertical axis. Contacting residues on the antigen and antibody are shown in red, except for Gln 121 shown in light purple. L chain residues that contact the antigen are labeled 1 (His 30), 2 (Tyr 32), 3 (Tyr 49), 4 (Tyr 50), 5 (Phe 91), 6 (Trp 92), and 7 (Ser 93). H chain residues that contact the antigen are labeled 8 (Thr 30), 9 (Gly 31), 10 (Tyr 32), 11 (Trp52), 12 (Gly 53), 13 (Asp 54), 14 (Arg 99), 15 (Asp 100), 16 (Tyr 101), and 17 (Arg 102); see Table 1. Lysozyme residues that contact the antibody are labeled 1 (Asp 18), 2 (Asn 19), 3 (Arg 21), 4 (Gly 22), 5 (Tyr 23), 6 (Ser 24), 7 (Leu 25), 8 (Asn 27), 9 (Lys 116), 10 (Gly 117), 11 (Thr 118), 12 (Asp 119), 13 (Val 120), 14 (Gln 121), 15 (Ile 124), and 16 (Leu 129). Gln 121 fits into the antibody surface pocket surrounded by V_L and V_H residues 2, 5, 6, 7, and 16 (Table 1).
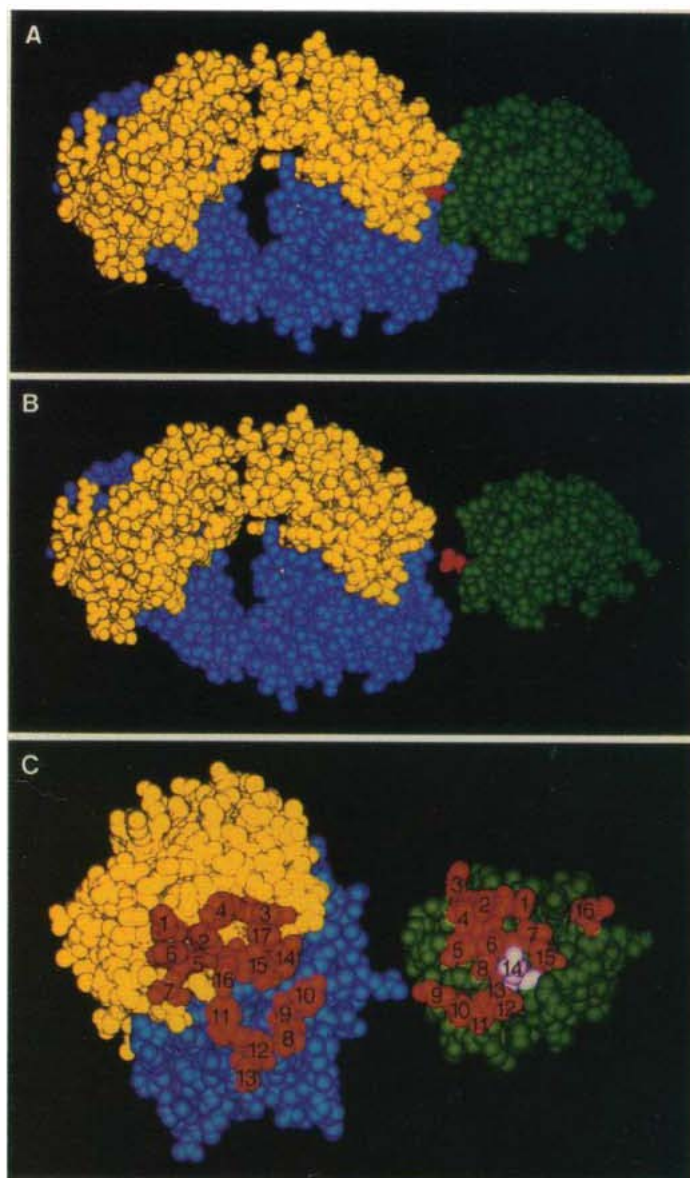
Fig. 4. Stereo diagram of the antibody-antigen interface in a similar orientation to Fig. 1. All atoms are shown for those residues involved in the interaction. Heavy and light main chains are indicated by thick and thin bonds, respectively, and hydrogen bonds by dotted lines. Lysozyme residues broadly lie below the diagonal from top left to lower right of the diagram.
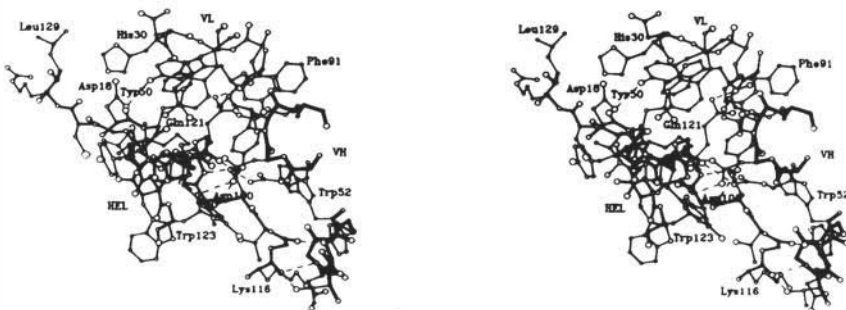
center of the surface lies near V_H CDR3, and is occupied by the side chain of V_H Asp 100, which forms H bonds to the side chains of Ser 24 and Asn 27 of lysozyme. Of the antibody hypervariable regions, V_L CDR2 contributes the least to antigen binding. A large number of antibody side chains in the interface (9 out of 15 if we exclude Gly residues) are aromatic, thus presenting large areas of hydrophobic surface to the antigen; in addition, some of them such as V_L Tyr 50 and V_H Tyr 101 participate in hydrogen bonding with the antigen via their polar atoms. In all, 748 Å^2 or about 11 percent of the solvent-accessible surface (24) of lysozyme is buried on complex formation, together with 690 Å^2 for the antibody.

Antigen variability and antibody specificity. The fine specificity of monoclonal antibody D1.3 for other avian lysozymes shows its ability to distinguish a single amino acid change in the antigen, at position 121. Fab D1.3 binds hen egg white lysozyme with an equilibrium affinity constant of $4.5 \times 10^7 M^{-1}$ (25). Bobwhite quail lysozyme, with four amino acid sequence differences (26) from hen lysozyme but none in the interface with Fab D1.3, binds with similar affinity (25). The binding of antibody D1.3 to the lysozymes of partridge [three amino acid differences (26)], California quail [four amino acid differences (26)], Japanese quail [six amino acid differences (27)], turkey [seven amino acid differences (28)], and pheasant and guinea fowl [ten amino acid differences each (29)] is undetectable $(K_A < 1 \times 10^5 M^{-1})$ with the enzyme-linked immunoabsorption assay used in our laboratory. These lysozymes differ from hen lysozyme in the amino acid residue at position 121, which makes close contacts with the antibody. Except for Japanese quail and pheasant lysozymes, all have Gln replaced by His.

Table 1. Antibody residues involved in contact with lysozyme. Sequence positions are numbered as in Kabat et al. (1) except for V_H CDR3, where the numbers of Kabat et al. (1) are given in parentheses.

Antibody residues		Lysozyme residues in contact
Light chain		
CDR1	His 30	Leu 129
	Tyr 32	Leu 25, Gln 121, Ile 124
FR2	Tyr 49	Gly 22
CDR2	Tyr 50	Asp 18, Asn 19, Leu 25
CDR3	Phe 91	Gln 121
	Trp 92	Gln 121, Ile 124
	Ser 93	Gln 121
Heavy chain		
FR1	Thr 30	Lys 116, Gly 117
CDR1	Gly 31	Lys 116, Gly 117
	Tyr 32	Lys 116, Gly 117
CDR2	Trp 52	Gly 117, Thr 118, Asp 119
	Gly 53	Gly 117
	Asp 54	Gly 117
CDR3	Arg 99 (96)	Arg 21, Gly 22, Tyr 23
	Asp 100 (97)	Gly 22, Tyr 23, Ser 24, Asn 27
	Tyr 101 (98)	Thr 118, Asp 119, Val 120, Gln 121
	Arg 102 (99)	Asn 19, Gly 22

A computer graphics analysis indicates that a His residue could be placed in the interface, in the space occupied by Gln 121, with small displacements of the contacting antibody side chains, maintaining the H bonds made by Gln 121. Conformational energy calculations (30) confirm this possibility, the total energy being little changed on substitution of His for Gln 121. The buried hydrogen bond is maintained with good geometry, and only very small shifts of neighboring groups are necessary to accommodate the mutation. This seems to rule out steric hindrance in explaining the absence of complex formation when His occurs at position 121. Other possible explanations for the effect of this amino acid substitution include the following. (i) His 121 could be charged, and consequently unstable in the hydrophobic pocket occupied by Gln 121; (ii) its side chain may have a different orientation from that of Gln, forming, for example, a salt bridge with Asp 119; and (iii) substitution of His for Gln at position 121 may induce a local change of conformation in the polypeptide backbone making the antigenic determinant unrecognizable by the antibody. Not enough information is available to decide on the relative importance of these factors. Nevertheless, the

Table 2. Lysozyme residues in contact with antibody.

Lysozyme residues	Antibody residues in contact (No.)	Lysozyme residues	Antibody residues in contact (No.)
Asp 18	1 L chain	Lys 116	3 H
Asn 19	2 H, L	Gly 117	6 H
Arg 21	1 H	Thr 118	2 H
Gly 22	4 H(3), L	Asp 119	2 H
Tyr 23	2 H	Val 120	1 H
Ser 24	1 H	Gln 121	5 H(1), L(4)
Leu 25	1 L	Ile 124	2 L
Asn 27	1 H	Leu 129	1 L

Table 3. Hydrogen bonded interactions between antibody and lysozyme. Sequence positions are numbered as in Kabat et al. (1) except for V_H CDR3 where the numbers of Kabat et al. (1) are given in parentheses.

	Antibody residue		Lysozyme residue	
Light chain				
	Nϵ2	His 30	O	Leu 129
	Oη	Tyr 50	Oδ1	Asp 18
	O	Phe 91	Nϵ2	Gln 121*
Heavy chain				
	Oγ1	Thr 30	O	Lys 116*
	N	Gly 31	O	Lys 116
	N	Gly 53	O	Gly 117*
	Nη1	Arg 99 (96)	O	Gly 22
	Oδ1	Asp 100 (97)	Nδ2	Asn 27
	Oδ2	Asp 100 (97)	Oγ	Ser 24 *
	Oη	Tyr 101 (98)	N	Val 120
	Oη	Tyr 101 (98)	N	Gln 121
	Oη	Tyr 101 (98)	Oδ1	Asp 119

*Denotes the closest interactions (distances < 2.5 Å)
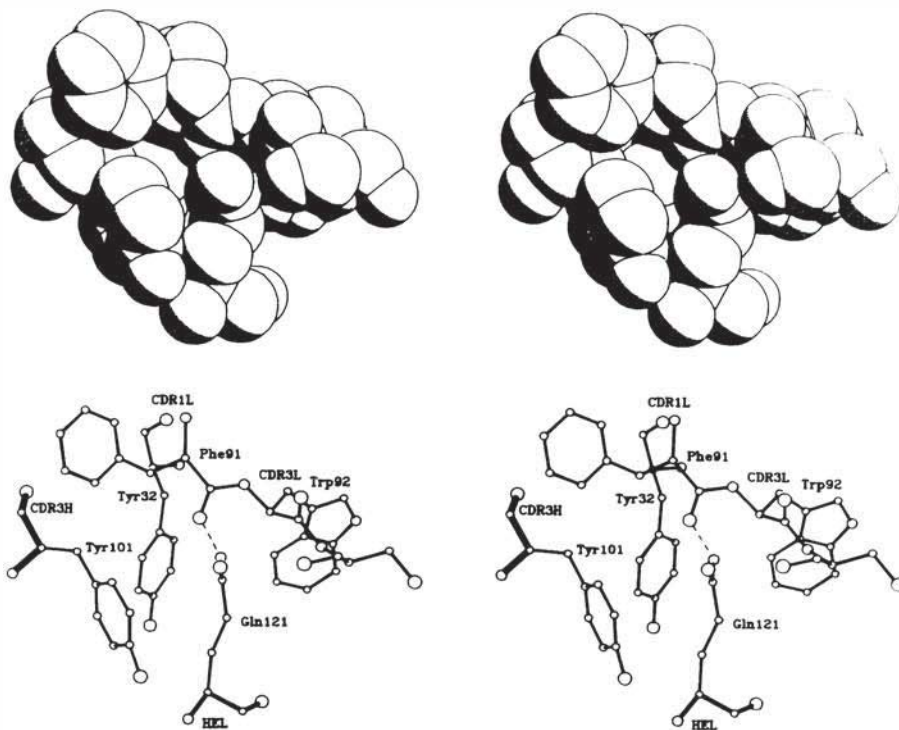
fact that the His residue is not induced to fit into the interface position occupied by Gln 121 is in agreement with a "lock and key" model (see below) of complex formation between conformationally stable antigen and antibody structures.

Japanese quail lysozyme has an Asn at position 121 and the additional differences Asn 19 → Lys and Arg 21 → Gln in the antigen-antibody interface. Asn 121 would be unable to form hydrogen bonds as strong as those of Gln 121. In addition, replacement of Asn 19 by Lys causes the loss of weak interactions between Oδ1 of Asn 19 and N of V_H Arg 102. The positively charged Lys 19 side chain would be repelled by V_H Arg 102 and would probably remain outside the interface, further reducing packing efficiency. Only main chain atoms of Arg 21 make contact with Fab and the side chain is external; therefore changes at this position in the antigen surface are probably not detrimental to complex formation.

The equilibrium affinity constant of Fab D1.3 binding of hen lysozyme is $4.5 \times 10^7 M^{-1}$. Other monoclonal antibodies to lysozyme that we (25) and others (31) have obtained and characterized show similar affinity constants for the homologous lysozyme antigen. Moreover, the determined equilibrium constants of protein antigens with their specific antibodies range from $10^5 M^{-1}$ to $10^{10} M^{-1}$ (32). Thus, D1.3 is a typical antibody of the monoclonal response in BALB/c mice and one of an about average affinity constant in immune responses to protein antigens in general.

Comparison of evolutionarily related proteins has been used to identify antigenic sites in proteins such as lysozyme (5, 25, 33). The detection of antigenic determinants by these fine specificity studies is biased toward the recognition of evolutionarily variable residues, such as Gln 121 by antibody D1.3. As our results show, such analyses are limited in defining antigenic determinants and, in particular, in defining the area of the antigen-antibody interaction, or even its center. Antigenic determinants have also been localized by measuring the reactivity of natural or synthetic peptides corresponding to different parts of the sequence of the protein with antibodies to the protein. This method cannot identify, or it can identify only partially, noncontinuous determinants such as those recognized by D1.3. Furthermore, given the large size of an

antibody combining site (about 690 Å² of accessible surface area in our study) plus the fact that only a small portion of the surface of a globular protein is made up of linear arrays of residues, the probability that all of the antigen residues contacted by a given antibody come from the same continuous segment of polypeptide chain is very low (34). Thus, most antibodies to native protein molecules probably recognize noncontinuous determinants.

In the three-dimensional structure of the antigen-Fab complex presented in this article, the axes of the V and C domains of Fab make an angle close to 180°. This gives an extended conformation, with the V and C domains further apart than they would be if that angle were smaller. This observation is not in agreement with hypotheses (35) in which the liganded antibody molecule is postulated to assume a more rigid conformation with an "elbow bending" angle (between the axes of the V and C domains) close to 120°. In fact, the angle observed in the lysozyme–Fab D1.3 complex corresponds to that postulated to occur in unliganded Fab's. Thus, the allosteric model of antibodies (35, 36) in which antigen binding induces changes in quaternary structure resulting in closer contacts across V and C domains is not consistent with the structure of this complex.

No other change of conformation in the antibody or antigen can be established by the present analysis. The classical "lock and key" metaphor (37) is an adequate simplification to describe the interaction of lysozyme and antibody D1.3. It implies that somatic recombination of the germline gene repertoire provides all the complementary antibody templates necessary to bind all possible antigens. These combining site templates preexist and are basically unaltered in binding their specific antigens. The lysozyme-D1.3 binding is accomplished by van der Waals and hydrogen bonding interactions, and the number of contacts is of the order of that seen in other protein-protein systems, with similar implications for the specificity and the energetics of the interacting molecules (23). Although the fit of the antigen-antibody contacting surface is remarkably good, there are some imperfections in the form of holes. One of these holes, between V_H residues 52 and 100 and lysozyme residues 24 and 118, is probably filled by a water molecule, hydrogen bonded to the N of lysozyme Gly 117 as suggested by an

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