Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become an urgent health concern.1,2 As of January 2021, approximately 110 million infections and more than 2.4 million deaths had been confirmed worldwide.3 Recently, the vaccines Tozinameran4,5 and mRNA-1273 developed by Pfizer-BioNTech and Moderna6,7, respectively, have been approved for emergency use by the Food and Drug Administration (FDA), which raises expectations for the convergence of COVID-19. However, herd immunity via a high percentage of the global population being vaccinated requires more time. Recently, highly infectious variants of SARS-CoV-2 were reported in the U.K., South Africa, Brazil, and other countries.8–10 Although the extent of the change in viral pathogenicity caused by these variants of concern is not fully understood, the effectiveness of in-use vaccines may become questionable for specific mutations. Therefore, combating this virus may continue for a long time, and more candidates for drugs and vaccines are urgently needed.

SARS-CoV-2 belongs to the family of betacoronaviruses, which comprise the spike, envelope, membrane, and nucleocapsid as structural proteins.11 Among the structural proteins, the spike glycoprotein (S-protein) mediates entry into the host cell via intermolecular interaction with human angiotensin-converting enzyme 2 (hACE2)12 at its receptor binding domain (RBD),13–16 making it a promising target for both antivirals and neutralizing antibodies. To date, numerous antibodies targeting the RBD of S-proteins have been reported.17–26 These antibodies can be classified into four categories on the basis of their binding sites (Figure 1a),22 Among them, antibodies that target RBD–hACE2 interaction sites as epitopes are considered particularly crucial, owing to the exceptions for the direct interruption of S-protein–hACE2 binding. Understanding the detailed binding modes of the RBD with currently reported antibodies/peptides17,18 can provide useful information for the design of more potent neutralizing antibodies and antiviral drug candidates.

So far, RBD–antibody/peptide interaction analyses have been conducted using molecular dynamics (MD) simulations. Luan et al. analyzed the interaction between the RBD and CB6 antibody by performing an alanine scan on the antibody side to reveal important residues on the RBD;19 Wang et al. focused on the hydrogen bond network and analyzed the interaction between the RBD and CC12.1 antibody to identify key epitopes in the RBD.20 Although many beneficial findings have
been obtained, these analyses often focused on hydrogen bonds as the most important interactions. Hydrophobic type of interactions, such as CH/π and π−π interactions, having significant impacts on binding, may not be evaluated quantitatively. It is desirable to apply ab initio quantum chemical calculations to accurately evaluate various interactions such as CH/π interactions, hydrogen bonding, and electrostatic interactions.

The fragment molecular orbital (FMO) method31−33 is one way to satisfy such requirements and has recently been applied to quantitatively and accurately evaluate molecular interactions.34−43 Our group comprehensively performed FMO calculations on each target of COVID-19-related proteins, registered the results in the FMO database (FMODB),44−46 and released the data for use by other researchers. Interaction analyses between S-protein and hACE2 or B38 Fab antibodies using the FMO method have been reported.47−49 This study focused on 12 antibodies/peptides (LCB1,27 LCB3,27 C10S,25 COVA2-04,31 BD-604,26 CB6,17 B38,17 BD-629,26 C102,22 CC12.3,19 CC12.1,19 and CV30) and analyzed the interactions between these antibodies/peptides and the RBD using the FMO method. To obtain more useful information for rational antibody design, we further estimated the importance of amino acid residues and regions in the RBD for antibody/peptide binding.

The complex structural data of the RBD and antibodies/peptides were obtained from the Protein Data Bank (PDB), and preparations were conducted (see the Supporting Information). Subsequently, the FMO calculation at the MP2/6-31G* level was conducted using the ABINIT-MP program.50,51 The interfragment interaction energy (IFIE) values of the complexes were obtained via FMO calculations. The IFIE values were further decomposed by the pair interaction energy decomposition analysis (PIEDA)55,56 calculation into four components: electrostatic (ES), exchange repulsion (EX), charge transfer with mixed terms (CT+mix), and dispersion (DI). These allow us to understand the detailed characteristics, which can be used to evaluate the key residues, such as epitopes, using the quantum chemical interaction energies of amino acid residue units. These results of FMO calculations and PIEDA analyses were registered in FMODB44−46 (Table S1) and are now available for FMODB users by querying FMODB ID or PDB ID.

The IFIE-sum, which was the sum of IFIEs between the RBD and antibodies/peptides, indicated that the estimated binding interaction energies between the RBD and antibodies/peptides showed a fairly good correlation with the experimental inhibitory activities (pIC50) of the antibodies/peptides ($R^2 = 0.540$ (Figure 1c and Table S1)). A stronger IFIE-sum estimated from FMO would indicate higher antiviral activities of antibodies/peptides targeting RBD.

We further investigated the importance of the RBD–antibody/peptide binding region, especially the interface residues. First, the antibody/peptide binding regions were selected per the EX, CT+mix, and DI value except ES.55,56 These values are only non-zero when close interactions, where the nearest atoms between two fragments are within twice the sum of their van der Waals radii, can be detected.57 The
residues binding the antibody/peptide were in two regions: Seq# 403−421 and the receptor binding motif (RBM, Seq# 438−506). The latter RBM is the major binding site of hACE2. The steric location of these two regions of one structure (PDB entry 7CH5) is shown in Figure 1b. These two regions are located at the interaction interface with the RBD−BD-629 Fab antibody and nearby regions. Previous research on the interaction between the SARS-CoV-2 S-protein RBD and ACE2 with FMO calculation also showed that the interaction sites of hACE2 on RBD could be concentrated in these two regions.

The contributions of residues in these two regions to the RBD−antibody/peptide interaction were investigated using the ratio of the IFIE-sum (Table S2). The ratio of the IFIE-sum of region 1 (Seq# 403−421) to the total IFIE-sum is approximately 40−50% (average of 47.3%). Although the number of residues in the region is small (19), the contribution is large. Similarly, the ratio of the IFIE-sum of region 2 (RBM) to the total IFIE-sum is approximately 40−60% (average of 53.4%), and it exceeds 50% in seven of the 12 structures treated in this study, indicating its large contribution. From the findings presented above, regions 1 and 2 play an important role in the RBD−antibody/peptide interaction in these complexes.

Next, to reveal important residues for molecular recognition between the RBD and antibody/peptide, we selected important residues meeting the criteria from these two regions for all complexes. For any ES, CT+mix, and DI components, the residues with interaction energies of less than −3 kcal/mol were considered important residues (Table S3). Fifty-two residues were identified as being important residues in at least one of the structures, while nine residues (i.e., T415, K417, Y421, F456, A475, F486, N487, N501, and Y505) were commonly detected as key residues in all complexes. Furthermore, these residues consist of two important interaction regions (Figure 2a and Tables S3 and S4). To examine how much these key residues contribute to the RBD−antibody/peptide interactions, we calculated the correlation between the pIC50 and IFIE-sums obtained from only these nine residues. The result showed a slightly higher correlation (R2 = 0.555), indicating that these residues can sufficiently account for the RBD−antibody/peptide interactions (Figure 1d and Table S5).

Next, the important residues in the RBD that were found in this study and those found in the previous report on the RBD−hACE2 interaction among SARS-CoV-2, SARS-CoV-2 chimera, and SARS-CoV were displayed and compared (Figure 2b). Most of the important RBD residues overlapped for RBD−antibody/peptide and RBD−hACE2 interactions (yellow-colored regions), except for two residues, N439 and L461. N439 and L461 were previously reported to be important for RBD−hACE2 interaction, but they are located at the binding edge. Therefore, we can say that the antibodies/peptides can inhibit hACE2 spatially via interaction with most of the important interaction points of hACE2 binding. Furthermore, regions outside the hACE2 binding sites are also used by antibodies/peptides as the epitopes (green-colored regions).

Finally, the interactions of the nine RBD residues with each amino acid residue of antibodies/peptides were analyzed using both IFIE and PIEDA values in detail. An analysis of the RBD and BD-629 Fab antibody complex (PDB entry 7CHS) was performed because this antibody has the best activity value among the antibodies calculated in this study (Table S1). The characteristics of the interactions at the interface between the

Figure 2. Important residues of the RBD for antibody/peptide binding. (a) The surface of RBD was colored according to the frequency of selected important residues in all of the samples. Darker red indicates higher frequency. (b) Confirmation and comparison of important RBD residues found in this study and a previous report on the RBD−hACE2 interaction. The surface map of important RBD residues for both antibodies/peptides and hACE2 interaction and for only antibody/peptide interaction are colored yellow and green, respectively. For any ES, CT+mix, and DI components, the residues with interaction energies of less than −3 kcal/mol were considered important residues (see Table S4).
RBD and BD-629 Fab, and XH/π interactions\textsuperscript{37,46,48,59} (X = C, O, and N) with aromatic amino acids, such as tyrosine and phenylalanine, and hydrogen bonds with the oxygen atom of the main chain were frequently observed. Figure 3 shows the structure around the nine key residues in the RBD and BD-629 Fab complex. Tables S6 and S7 list the hydrogen bond and XH/π interaction energies and their characteristic distances between each fragment for nine residues by IFIE and PIEDA. Hydrogen bonds between side chains were also observed. The hydrogen bonds formed between the RBD and BD-629 Fab could be categorized into four types based on Figure 3 and Table S6. The first was hydrogen bonds between the side chains of the neutral amino acid residues. The IFIEs between residues containing such hydrogen bonds were approximately $-13$ to $-14$ kcal/mol, specifically fragment pairs such as T415spike-Y58H (IFIE = $-13.0$ kcal/mol) and N501spike-S30L (IFIE = $-14.0$ kcal/mol) from panels a and h of Figure 3, respectively. Second, the IFIEs between residues that contained a charged side chain on one of the amino acid residues that formed hydrogen bonds between the side chains were confirmed to be larger than the IFIEs of the first type because of the electrostatic interaction. Specifically, fragment pairs such as N487spike-E26H (IFIE = $-25.8$ kcal/mol) and N487spike-R97H (IFIE = $-25.1$ kcal/mol) were formed, as shown in Figure 3g. Third, when both amino acid residues contained charged side chains, the number of electrostatic interactions of salt bridges and the number of hydrogen bonds were much larger than the former two types, and the corresponding IFIE between K417spike and D101H was $-153.1$ kcal/mol (although the hydrogen bond between the K417spike side chain and the oxygen atom of the main chain on D101H was also included), as shown in Figure 3b. Finally, when hydrogen bonds were formed between the side chain and the oxygen atom of the main chain, the IFIEs were less than $-20$ kcal/mol, specifically, fragment pairs containing hydrogen bonds between the oxygen atom on F456spike and the Y33H side chain (IFIE = $-23.7$ kcal/mol) (Figure 3d), between the oxygen atom on Gly476spike (assigned as the A475spike fragment) and the N32H side chain (IFIE = $-20.9$ kcal/mol) (Figure 3e), and between the Y505spike side chain and oxygen atom on V29L (IFIE = $-20.9$ kcal/mol) (Figure 3i). On the contrary, many π-orbital interactions were observed around aromatic amino acid residues, which can be classified into two categories: the OH/π interaction and CH/π interactions. First, ES and DI values were similar between residues where the OH/π interaction was formed (see Table S7 for each energy component), specifically, a fragment pair such as Y421spike-Y33H (Figure 3c). On the contrary, in many cases, DI was the main component between residues where CH/π interactions were formed (Table S7), specifically, fragment pairs such as Y456spike-Y99H, F486spike-Y106H, and Y505spike-F32H (panels d, f, and i, respectively, of Figure 3).

In the Supporting Information, we explained the binding mode around the key residues in detail. Here, the corresponding FMODB data regarding the detailed energy components between individual residues by IFIE/PIEDA can be referenced using the FMODB ID\textsuperscript{44} (Table S1).

As described above, we found that the nine key residues on the RBD strongly interact with the antibody residues regarded as the epitopes via various binding modes such as electrostatic interactions, hydrogen bonding, and π-orbital interactions (Figure 3). Here, the aromatic amino acids Y421, F456, F486,
Example of a computational model (PDB entry 6XCM) (Figure S1) (only the monomeric RBD-antibody/peptide was preserved for the FMO calculation), structural information about each calculation model and interaction energies for RBD-antibody/peptide interactions (Table S1), IFIE-sum of region 1 (R403–Y421), region 2 (RBM), and All (RBD) and the ratio of the IFIE-sum of region 1 or region 2 to the total IFIE-sum (Table S2), relationship between residues on the RBD and the number of structures identified as important residues (Table S3), PIEDA results of antibody/peptide residues on the RBD (only region 1 (Seq# 403–421) and region 2 (RBM)) (Table S4), interaction energies among the nine key residues on the RBD and antibodies/peptides (Table S5), XH–Y hydrogen bonds between nine key residues on the SARS-CoV-2 RBD and BD-629 Fab (Table S6), and XH/π interactions between nine key residues with the SARS-CoV-2 RBD and BD-629 Fab (Table S7) (PDF)

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcl.1c00663.

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Notes

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