

1 Inhibitor compound potential parameters

In the table below, the potential parameters for compound 2 are given. Atom numbers are as specified in Fig. 1, and each atom is specified as a CHARMM22 atom type and an associated charge. Carbon atoms not specified in the figure/table are treated as CA atom types in the CHARMM22 force field with 0 charge.

Table 1: Potential parameters for compound 2.

Atom number	CHARMM22 atom type	charge
1	CT1	0.140
2	HA	0.090
3	CT2	0.000
4	CA	-0.115
5	CA	-0.115
6	CA	-0.115
7	CA	-0.115
8	CA	0.000
9	CA	-0.115
10	HP	0.115
11	HP	0.115
12	HP	0.115
13	HP	0.115
14	HP	0.115
15	CA	-0.115
16	CA	-0.115
17	CA	-0.115
18	CA	-0.115
19	CA	0.000
20	CA	-0.115
21	HP	0.115
22	HP	0.115
23	HP	0.115
24	HP	0.115
25	HP	0.115
26	OH1	-0.660
27	H	0.430

2 Constructing the water box in the cavity region.

In this section, the technical details of the algorithm for constructing a rectangular box within the protease cavity for calculating the water density are presented.

First, a coordinate system is chosen in which the z -axis is defined by taking the unit vector along the line connecting the center-of-mass between the two C_α atoms of Pro 81 and Pro 81' (see Fig. 2) and the center-of-mass of the two C_α atoms of Gln 7 and Gln 7', and the y -axis is defined by taking the component of the vector connecting the C_γ atoms of Val 32 and Val 32' perpendicular to the z direction and generating a unit vector from the result. Finally, the x -axis is obtained from the cross product of the unit vectors along the y and z directions thus defined.

Next, the height of the box is defined as the projection along the z -axis defined by the line connecting the center-of-mass between the two OD2 atoms of Asp 25 and Asp 25' and the center-of-mass of the two C_β atoms of Ile 50 and Ile 50'. The box width is defined as the projection along the y -axis defined by the line connecting the C_γ atoms Val 32 and Val 32', respectively. Finally, the box depth is defined as the projection along the x -axis defined above of the line connecting the C_α atoms of Pro 81 and Pro 81'.

This definition ensures that the z -axis is always the C_2 symmetry axis of the enzyme and ensures that the lines used to compute the height and width of the box are always nearly parallel and perpendicular to the z -axis, respectively, differing from these orientations by only a few degrees on average.

Figure 1: Depiction of compound 2 including atom labels specified in Table 1.

Figure 2: Illustration of the algorithm used to determine the water box dimensions. Residues referred to are indicated in the figure, and the resulting box is shown.



