SUPPORTING INFORMATION

3D interaction homology: Hydropathic interaction environments of serine and cysteine are strikingly different and their roles adapt in membrane proteins.

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Figure S11: Hydropathic interaction maps illustrating the Gaussian-weighted average clustered SERm (serine, membrane protein) sidechain environments for the *f6.300* chess square/parse.

Figure S12: Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYSm (cysteine, membrane protein) sidechain environments for the *d5.300* chess square/parse.

Figure S13: Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYSm (cysteine, membrane protein) sidechain environments for the *f6.300* chess square/parse.

Figure S1. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered SER sidechain environments for the *c5* chess square. A) 60° parse; B) 180° parse; C) 300° parse. Two views are shown for each map: left) the CA-CB z-axis points out of the page, right) the CA-CB axis points up. The x-axes of both views point right and the y-axis points up on the left and back on the right. The blue contours represent favorable polar interactions between the hydroxyl and neighboring residues; red contours are unfavorable polar interactions; green contours are favorable hydrophobic-hydrophobic interactions between the methylene and neighbors; purple contours are unfavorable hydrophobic-polar interactions. Translucent green contours, when present, are plotted at one-half the map density of the solid green contours.

Figure S2. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered SER sidechain environments for the *d5* chess square. A) 60° parse; B) 180° parse; C) 300° parse. See caption for Figure S1.
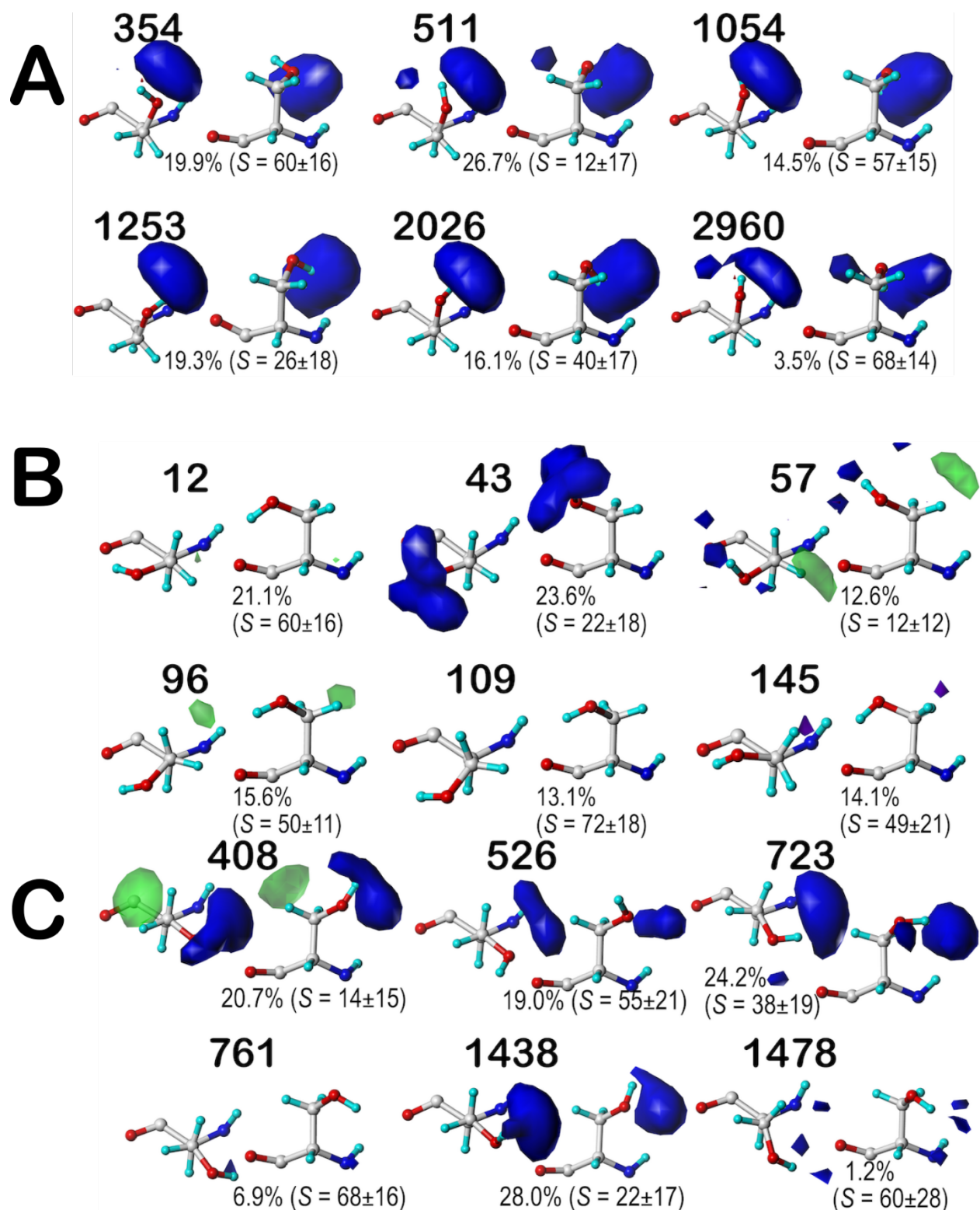
Figure S3. **Hydropathic interaction maps illustrating the Gaussian-weighted average clustered SER sidechain environments for the *f6* chess square. A) 60° parse; B) 180° parse; C) 300° parse.** See caption for Figure S1.

Figure S4. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYS sidechain environments for the *c5* chess square. A) 60° parse; B) 180° parse; C) 300° parse. See caption for Figure S1.
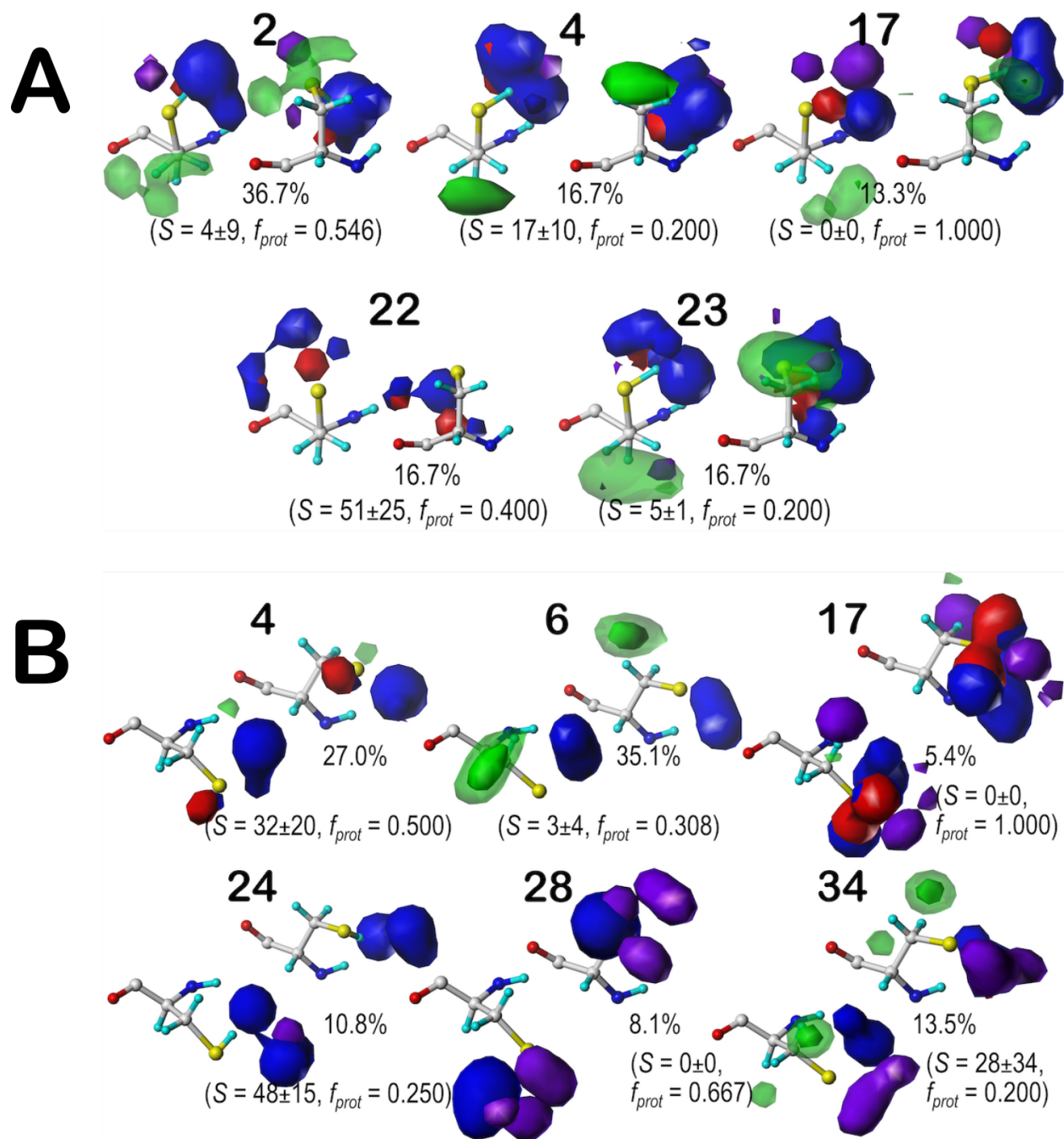
Figure S5. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYS sidechain environments for the *d5* chess square. A) 60° parse; B) 300° parse. See caption for Figure S1.
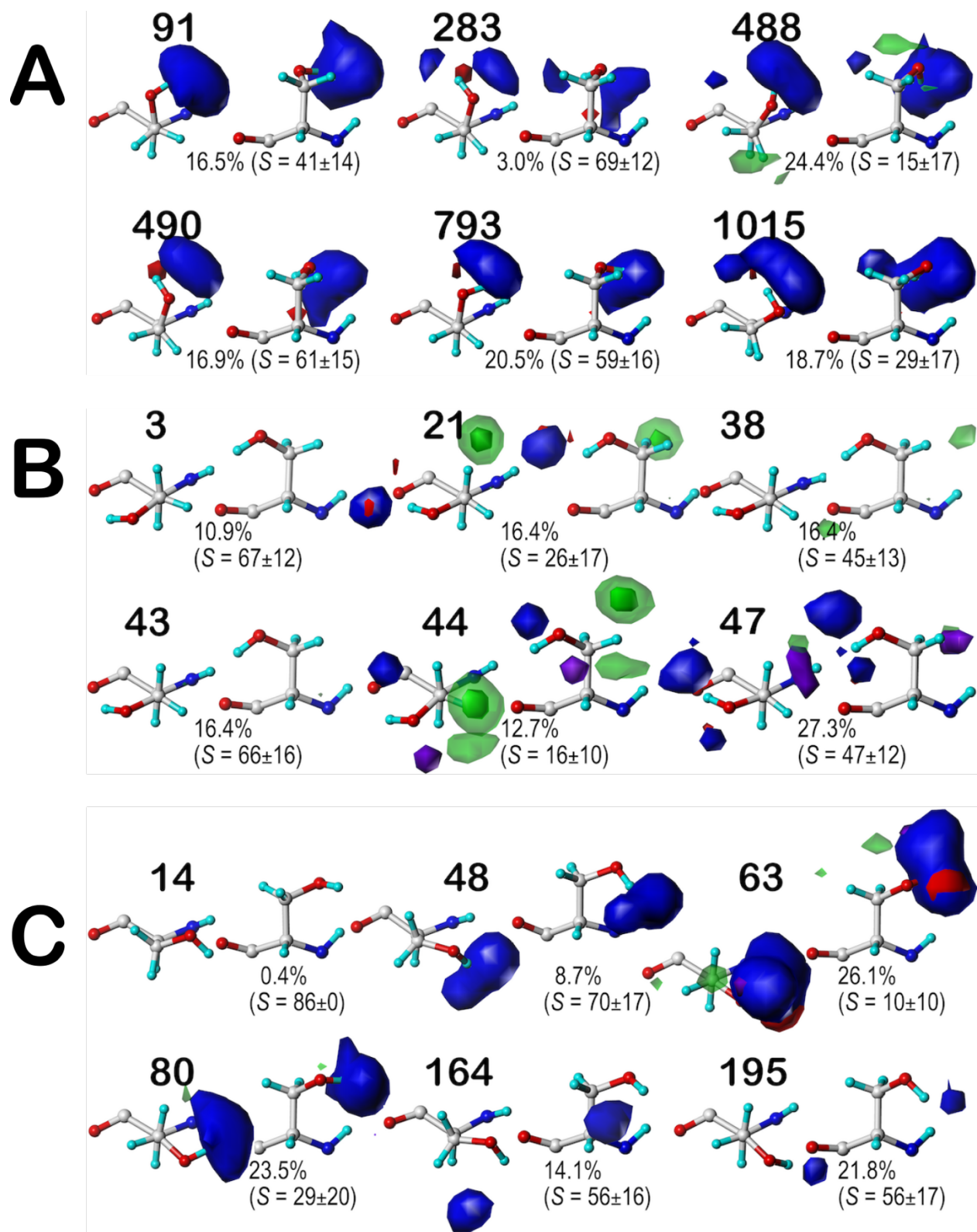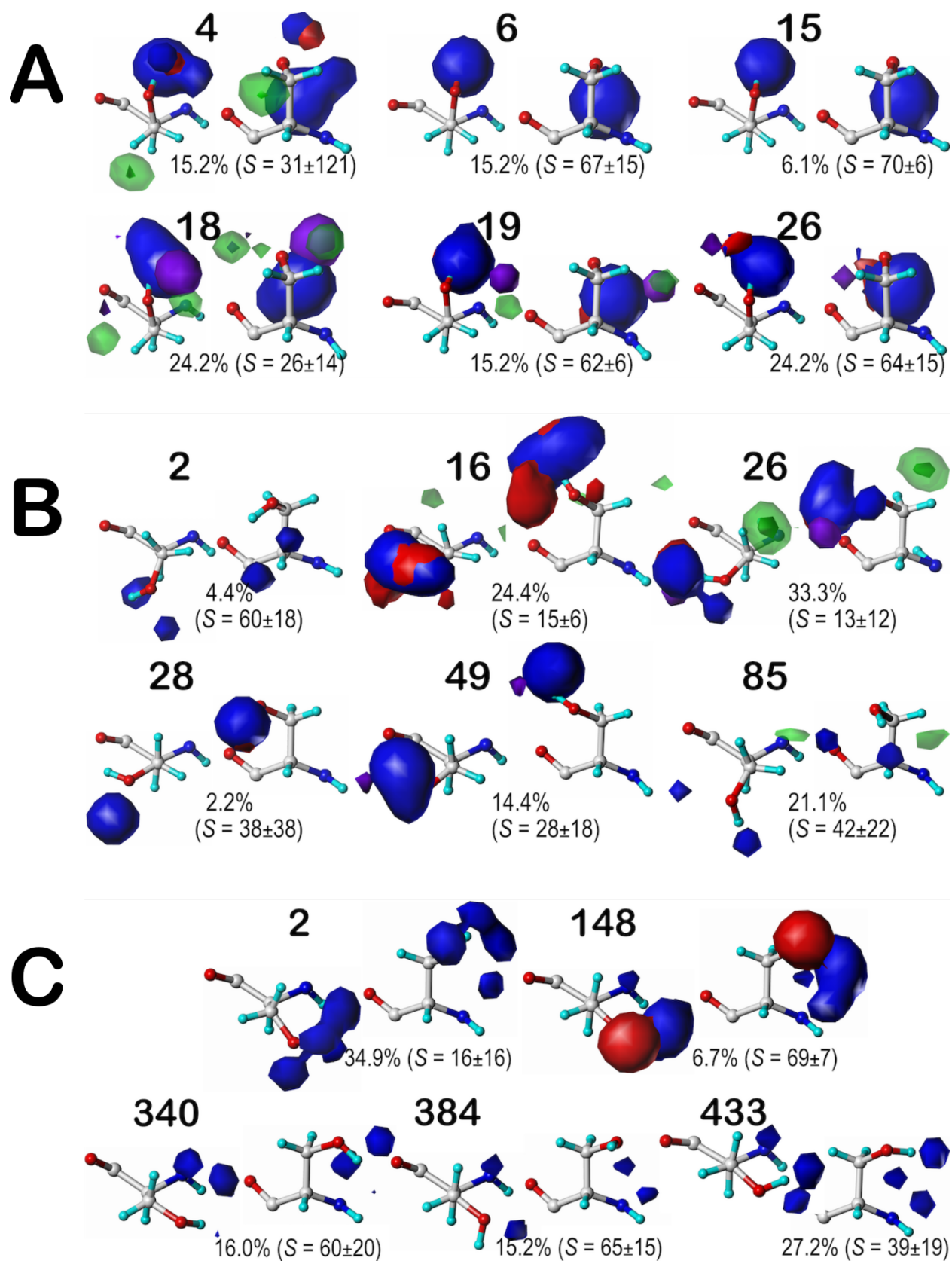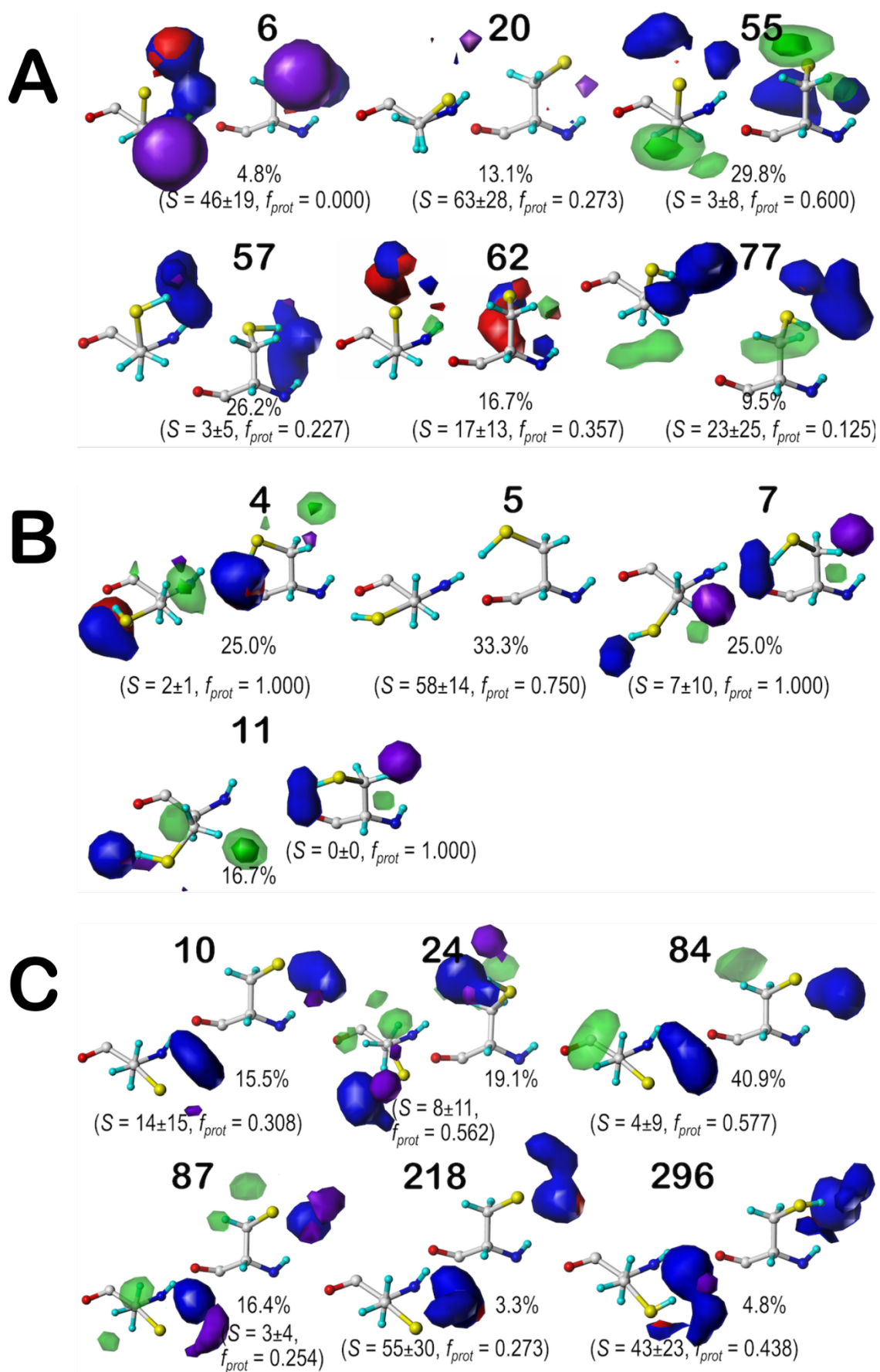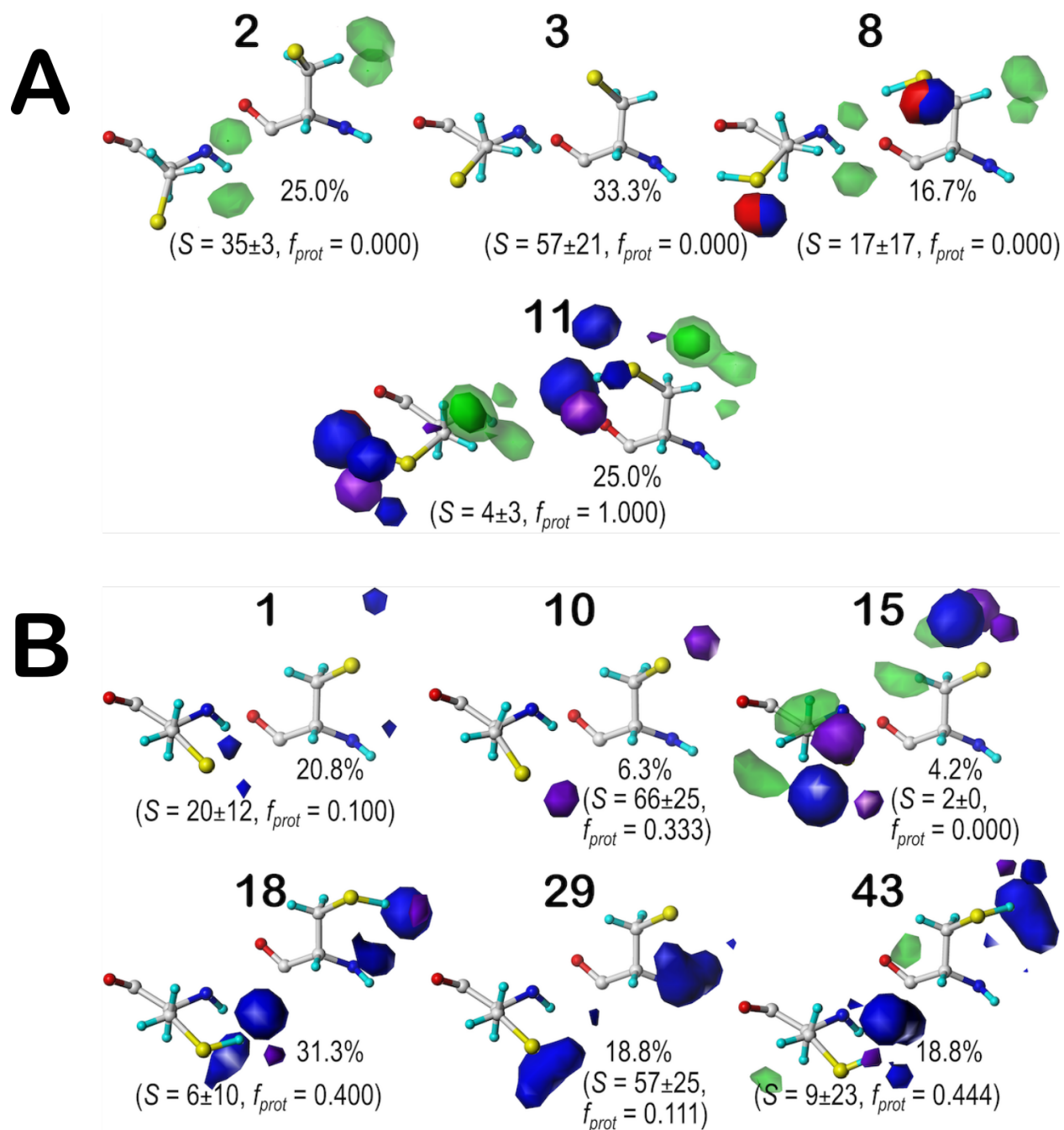
Figure S6. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYS sidechain environments for the *f6* chess square. A) 180° parse; B) 300° parse. See caption for Figure S1.
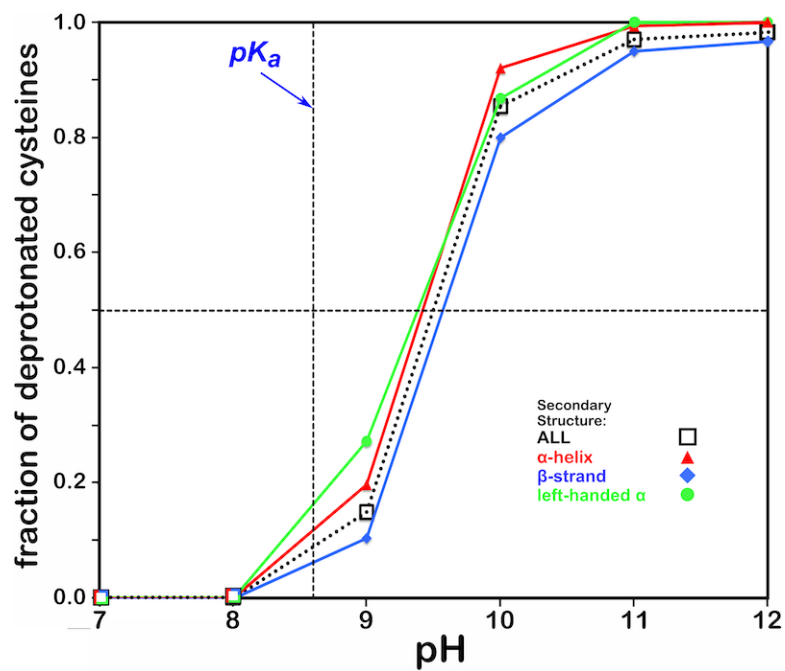
Figure S7. Titration curves of CYZ (cysteine, broken bridge) residue by secondary structure. The native pK$_a$ for cysteine is indicated.

32 2.8% (*S* = 0±0)

96 4.7% (*S* = 8±5)

100 10.9% (*S* = 4±7)

122 10.4% (*S* = 16±16)

136 2.8% (*S* = 7±8)

148 5.2% (*S* = 16±13)

154 0.4% (*S* = 0±0)

165 1.4% (*S* = 11±1)

171 58.3% (*S* = 0±0)

175 2.8% (*S* = 0±0)

Figure S8.   Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYX (cysteine, intact bridge) sidechain environments for the *b1.60* chess square/parse. See caption for Figure S1.
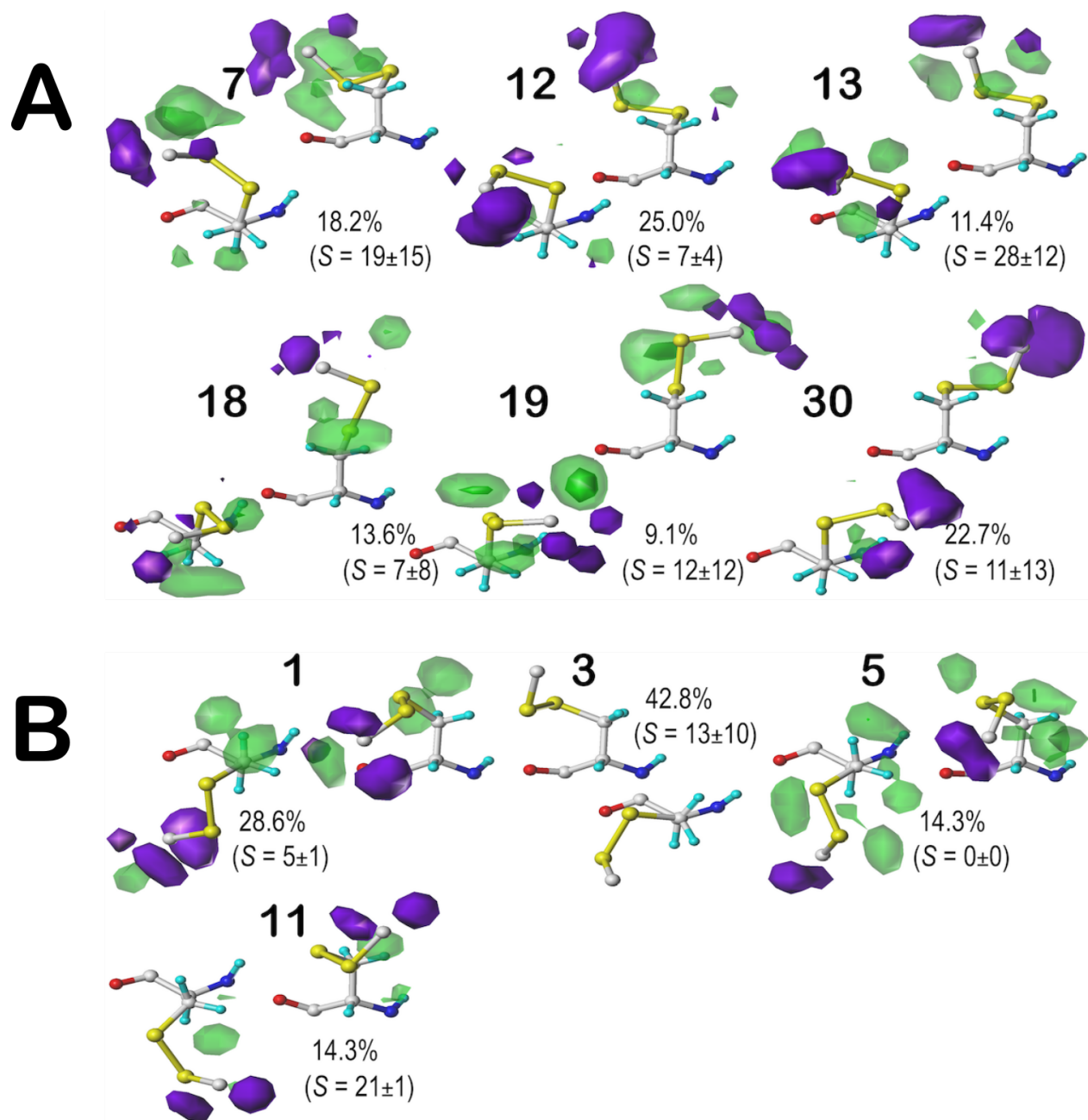
Figure S9. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYX (cysteine, intact bridge) sidechain environments for the *c5* chess square. A) 60° parse; B) 180° parse. See caption for Figure S1.

C

27 10.1% ($S = 3\pm6$)

29 3.2% $S = 13\pm12$)

32 4.8% ($S = 1\pm1$)

117 3.6% ($S = 19\pm17$)

222 20.5% ($S = 8\pm10$)

302 23.3% ($S = 2\pm1$)

316 5.0% ($S = 15\pm15$)

332 17.9% ($S = 6\pm14$)

335 7.2% ($S = 7\pm7$)

400 4.2% ($S = 8\pm14$)
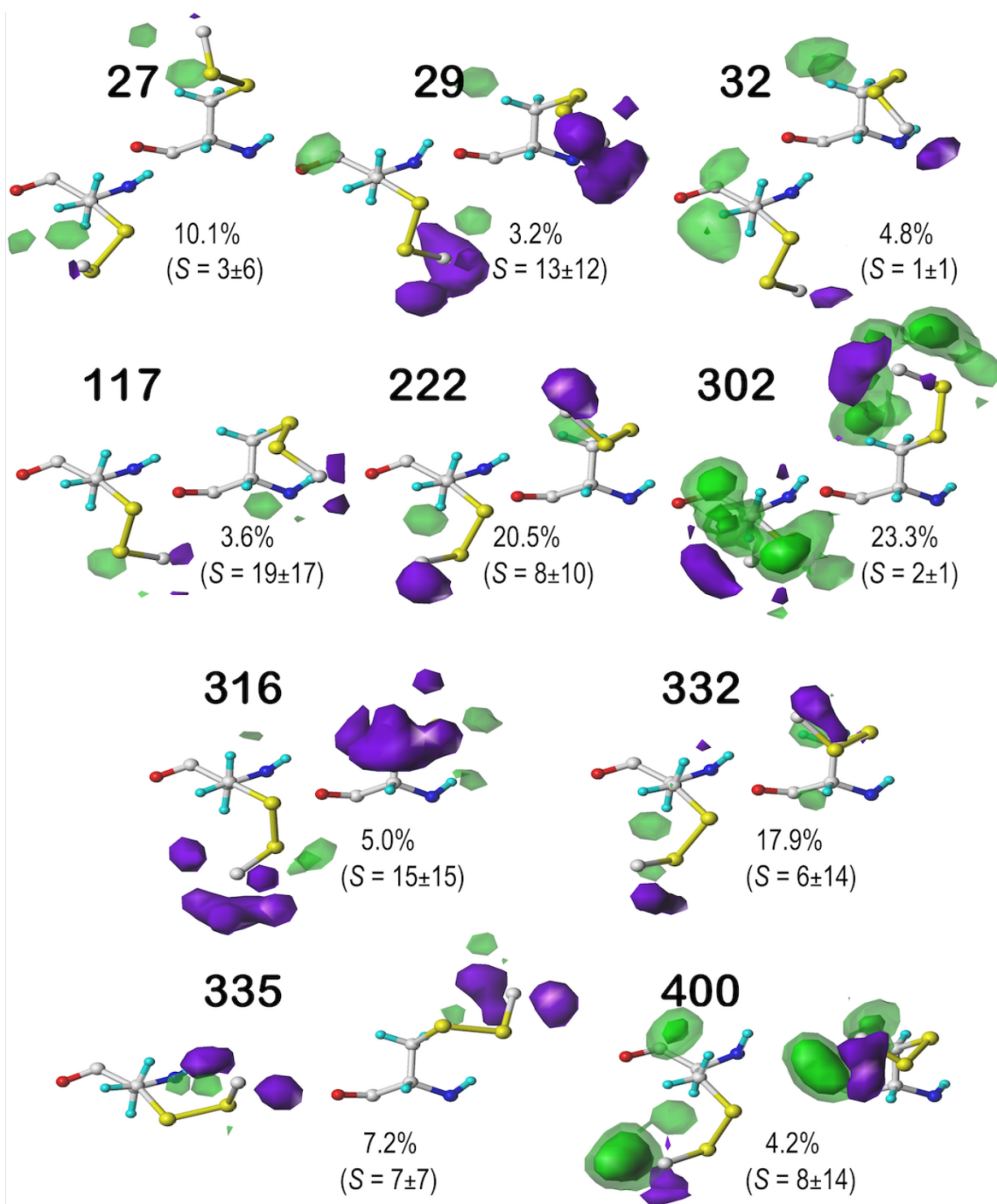
Figure S9 (continued). **C) 300° parse.** See caption for Figure S1.

39

f_{lipid} = 0.054/0.078/0.059/0.013

17.9%
($S = 13\pm18$)

90

f_{lipid} = 0.006/0.085/0.023/0.064

3.7%
($S = 81\pm2$)

91

f_{lipid} = 0.057/0.081/0.019/0.024

29.0%
($S = 12\pm16$)

96

f_{lipid} = 0.006/0.025/0.008/0.014

6.2%
($S = 63\pm24$)

115

f_{lipid} = 0.056/0.120/0.055/0.036

19.1%
($S = 52\pm20$)

145

f_{lipid} = 0.070/0.106/0.076/0.037

24.1%
($S = 38\pm14$)

Figure S10. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered SERm (serine, membrane protein) sidechain environments for *d5.300* chess square/parse. f_{lipid} values are the fraction of all interaction scores arising from residue-to-lipid interactions in the molecular models by type (green-favorable hydrophobic, purple-unfavorable hydrophobic, blue-favorable polar, red-unfavorable polar). See also caption for Figure S1.

9

f_{lipid} = 0.056/0.113/0.008/0.019

5.9%
($S = 73\pm3$)

37

f_{lipid} = 0.000/0.000/0.000/0.000

7.1%
($S = 34\pm14$)

40

f_{lipid} = 0.004/0.013/0.000/0.000

17.6%
($S = 58\pm6$)

62

f_{lipid} = 0.000/0.000/0.000/0.000

9.4%
($S = 58\pm11$)

65

f_{lipid} = 0.012/0.064/0.050/0.045

14.1%
($S = 45\pm9$)

78

f_{lipid} = 0.064/0.103/0.081/0.051

45.9%
($S = 16\pm16$)

Figure S11. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered SERm (serine, membrane protein) sidechain environments for *f6.300* chess square/parse. See captions for Figures S1 and S10.
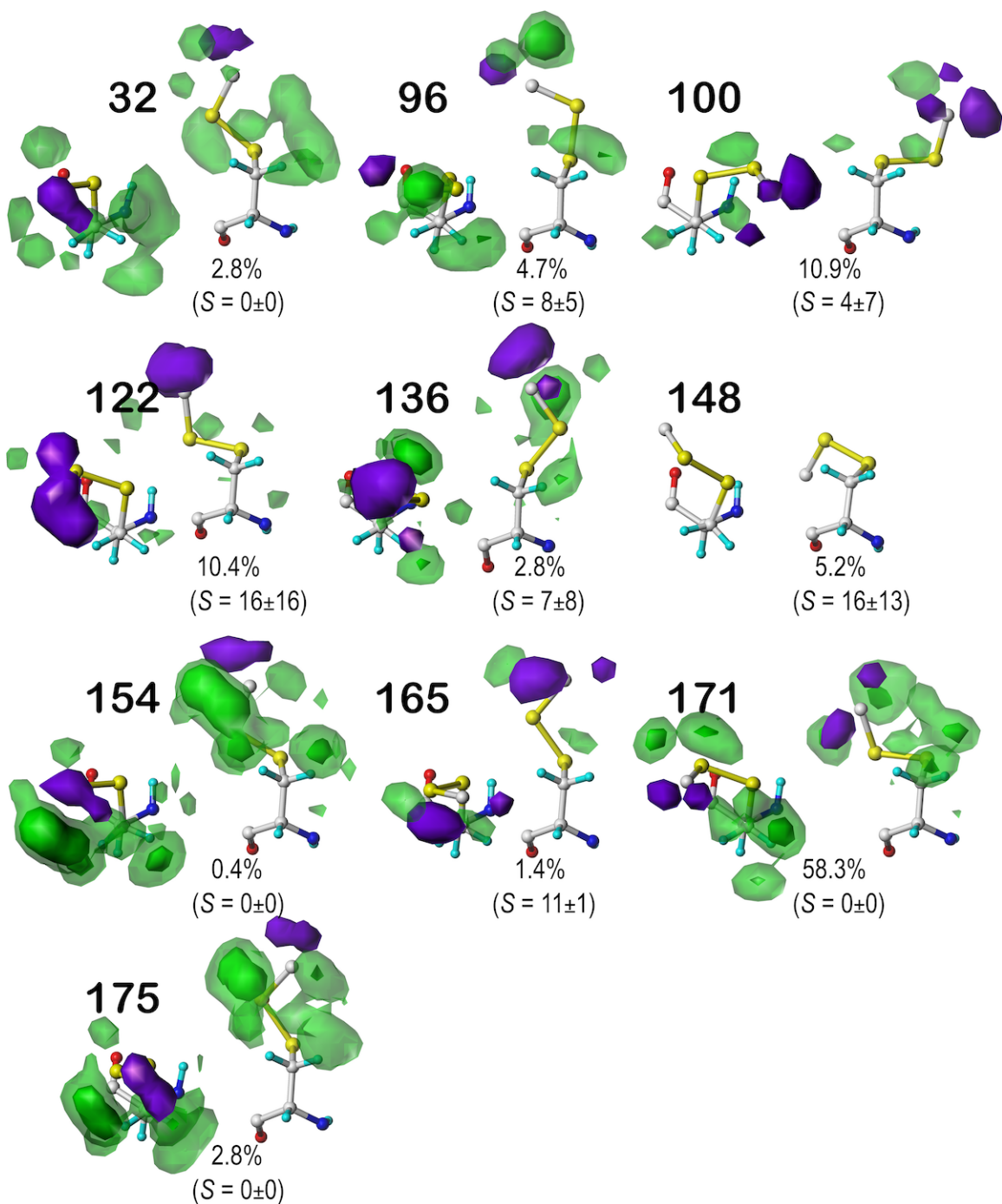
7
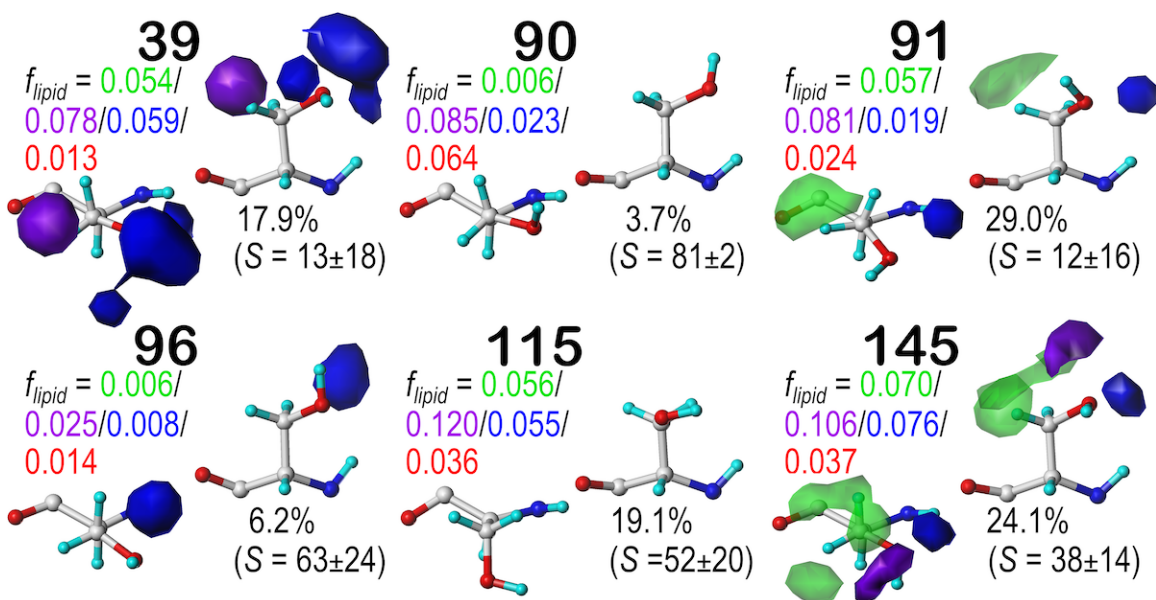
f_{lipid} = 0.045/0.060/0.009/0.060

21.9%

(S = 7±13, f_{prot} = 0.426)

81

f_{lipid} = 0.223/0.180/0.113/0.073

5.7%

(S = 28±33, f_{prot} = 0.214)

93

f_{lipid} = 0.176/0.146/0.038/0.108

17.4%

(S = 24±25, f_{prot} = 0.349)

123

f_{lipid} = 0.125/0.081/0.049/0.021

6.9%

(S = 22±25, f_{prot} = 0.471)

183

f_{lipid} = 0.054/0.077/0.067/0.055

5.7%

(S =38±34, f_{prot} = 0.214)

189

f_{lipid} = 0.024/0.034/0.003/0.030

7.3%

(S = 32±20, f_{prot} = 0.111)

200

f_{lipid} = 0.054/0.065/0.019/0.017

17.4%

(S = 8±13, f_{prot} = 0.488)

234

f_{lipid} = 0.065/0.066/0.008/0.018
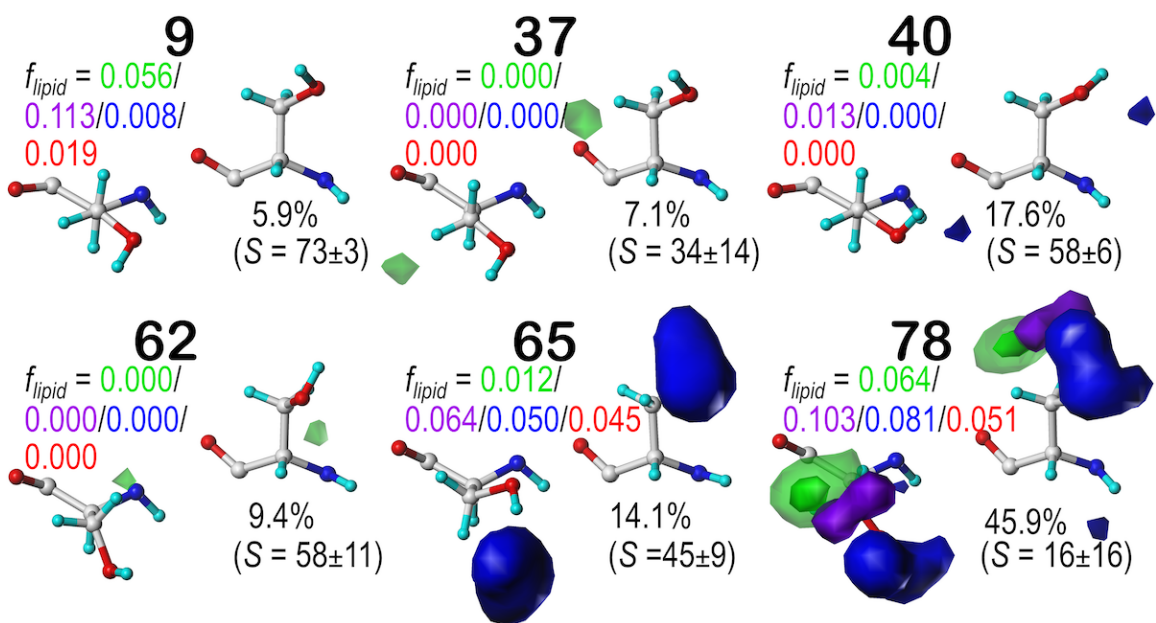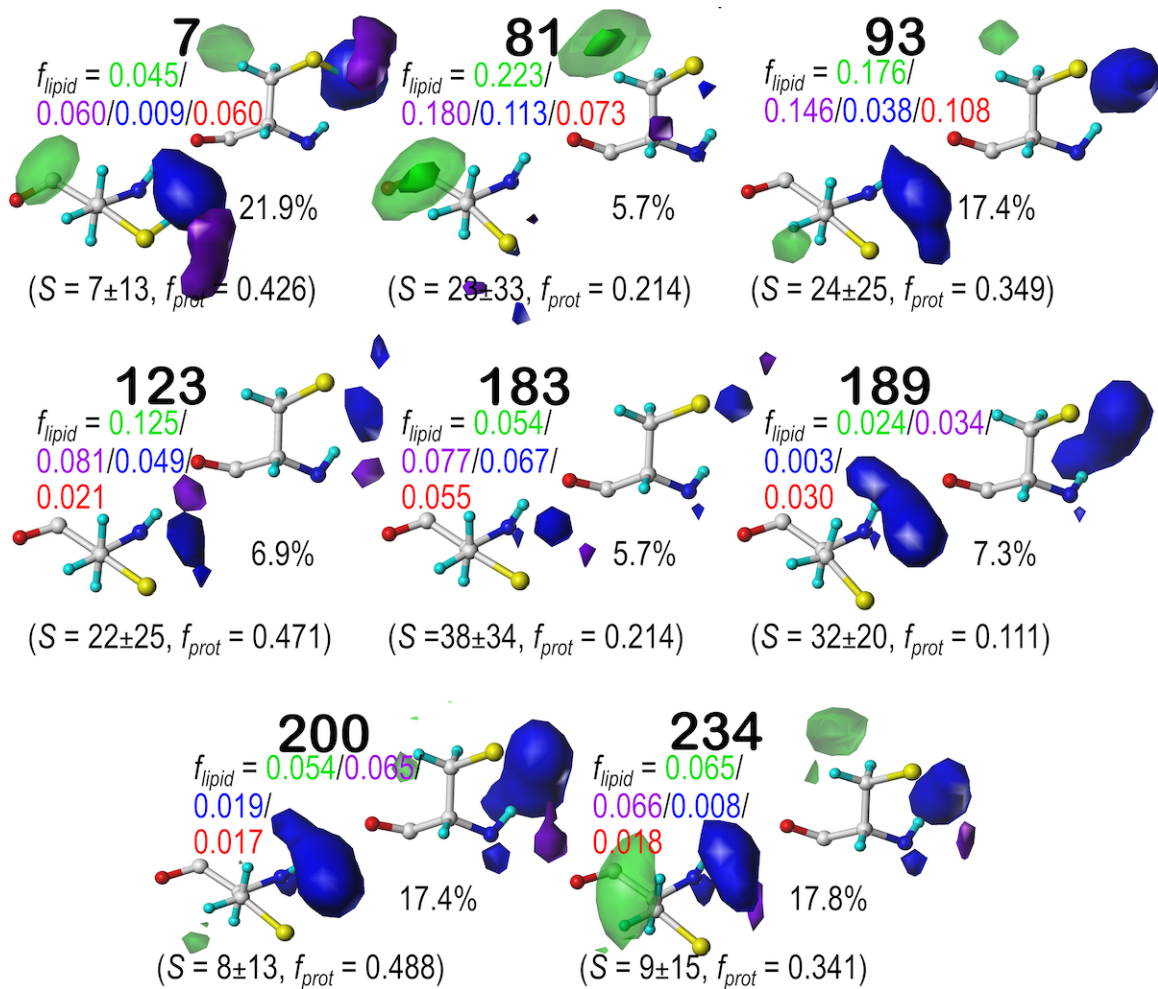
17.8%

(S = 9±15, f_{prot} = 0.341)

Figure S12. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYSm (cysteine, membrane protein) sidechain environments for *d5.300* chess square/parse. See captions for Figures S1 and S10.
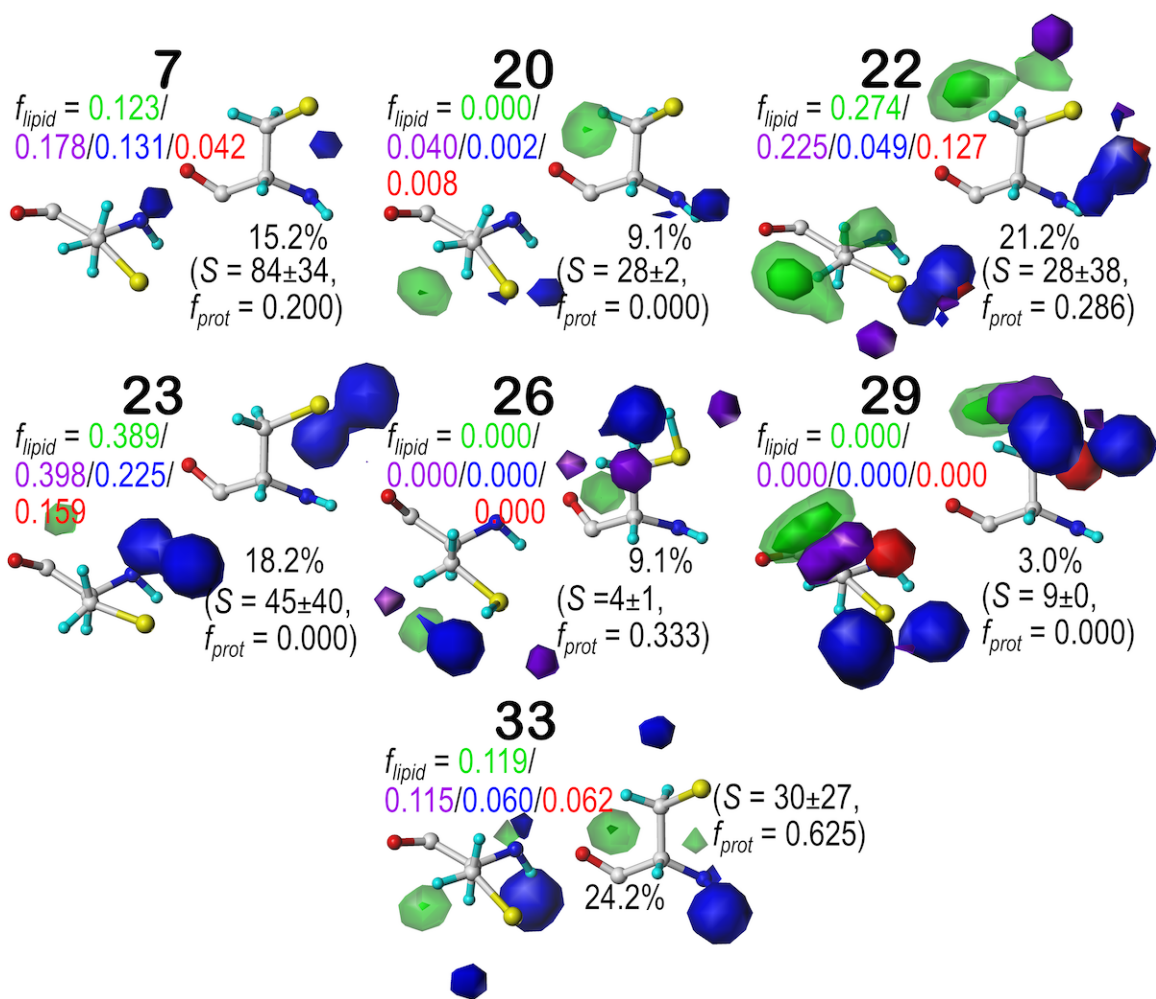
Figure S13. Hydropathic interaction maps illustrating the Gaussian-weighted average clustered CYSm (cysteine, membrane protein) sidechain environments for *f6.300* chess square/parse. See captions for Figures S1 and S10.