Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

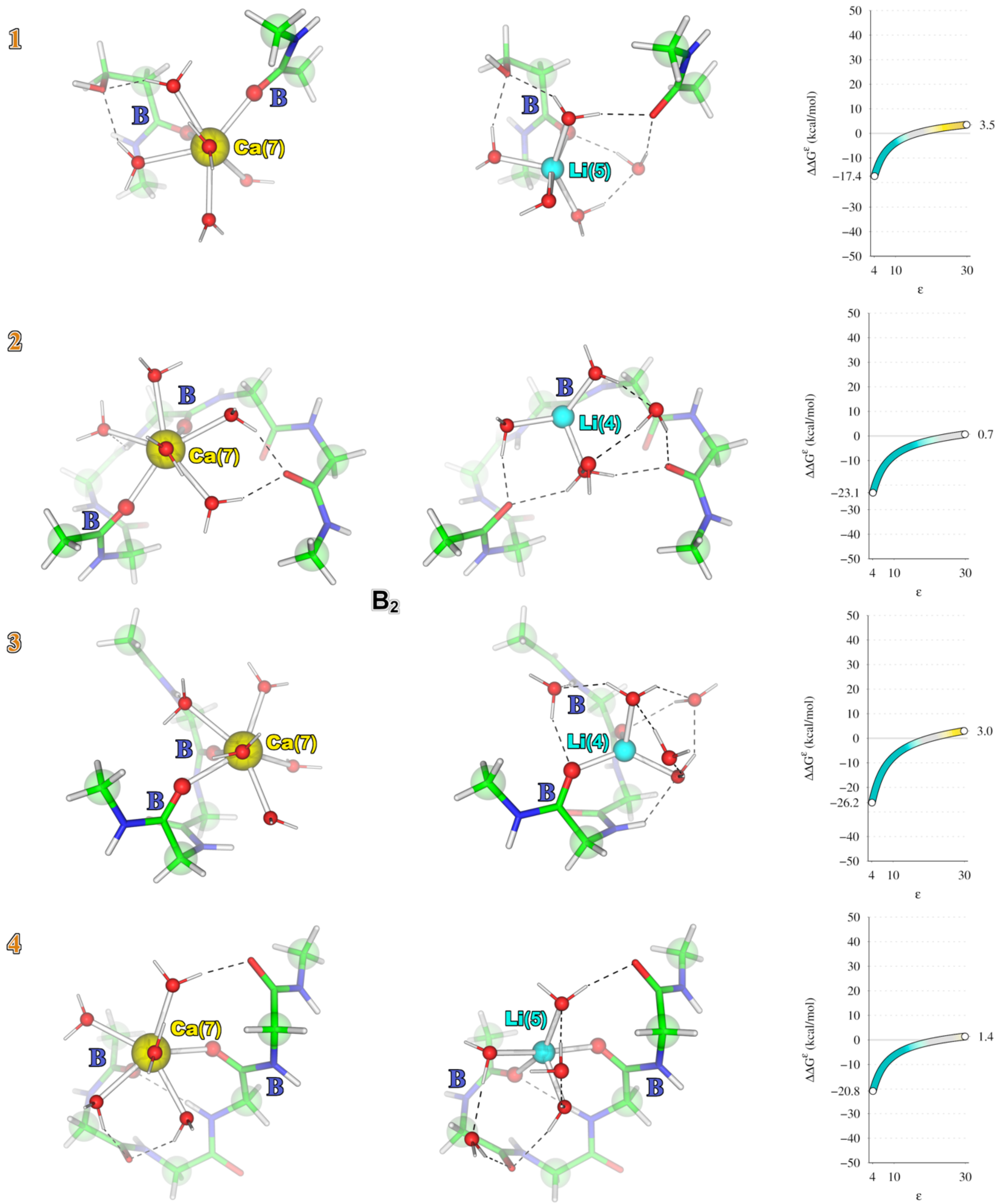
Factors Allowing Small Monovalent Li^{+} to Displace Ca^{2+} in Proteins

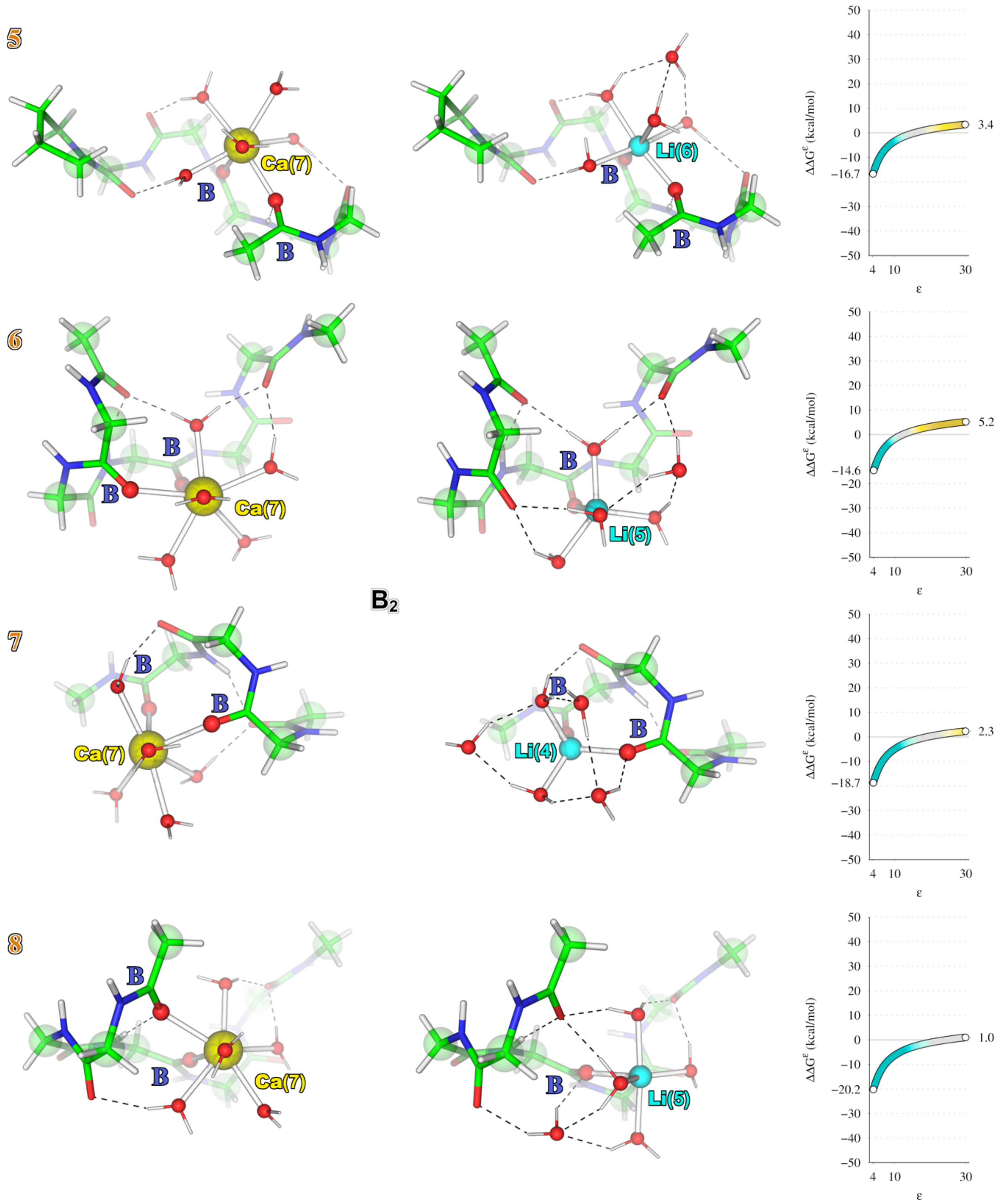
Cédric Grauffel[†*], Wei-Hsiang Weng[†], Carmay Lim[†,‡,*]

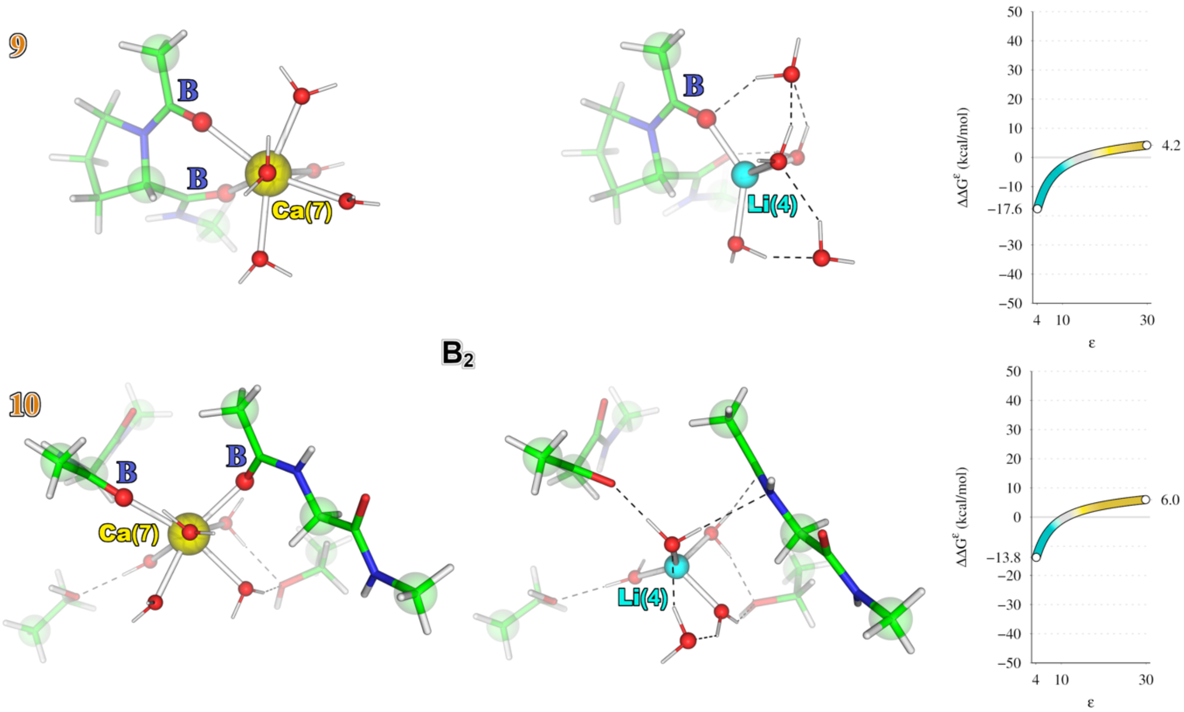
[†]Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan

[‡]Department of Chemistry, National Tsing Hua University, Hsinchu 300 Taiwan

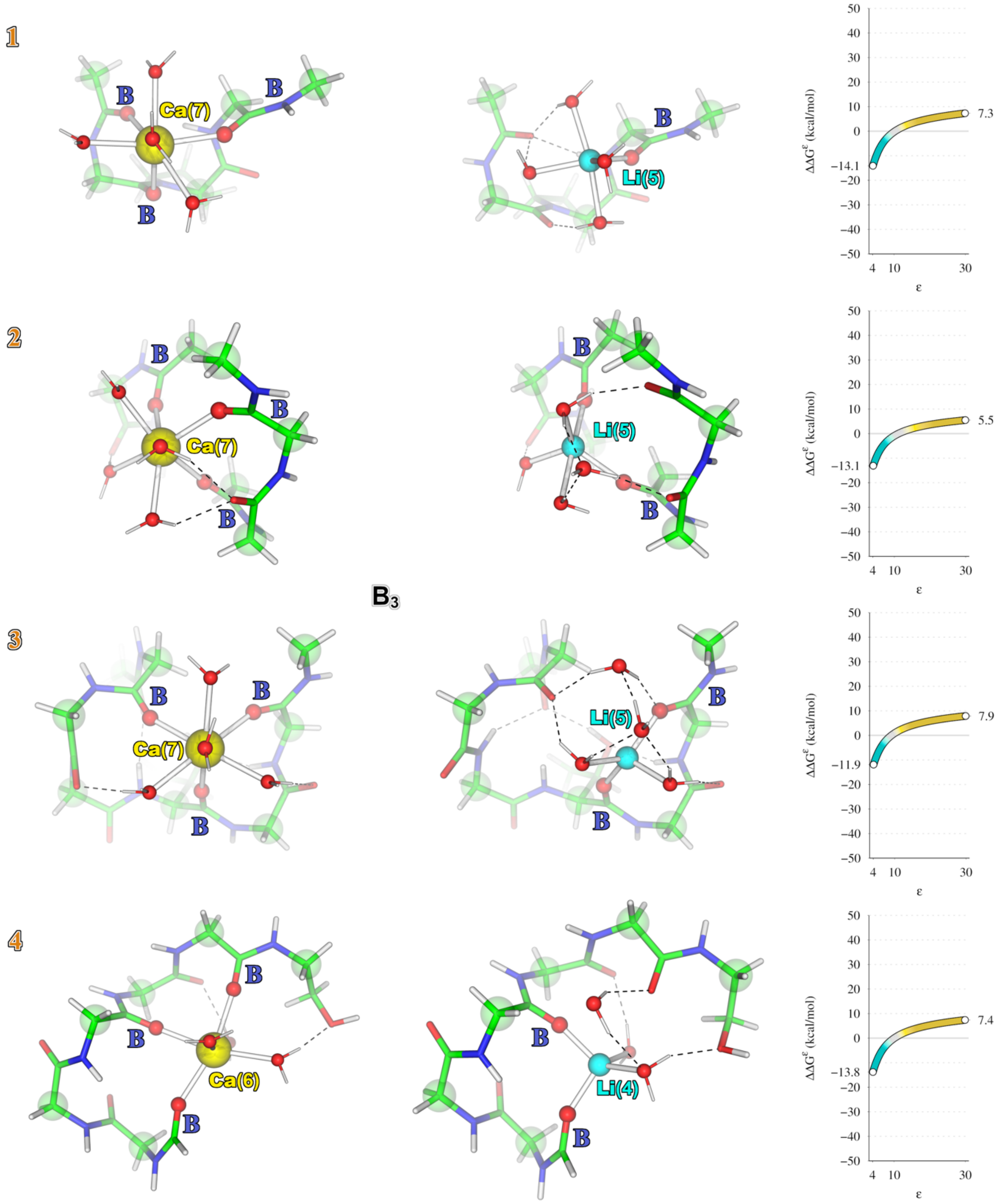
Supporting Information Figure S1a. Models for B_2 Ca^{2+}-sites containing two backbone ligands.

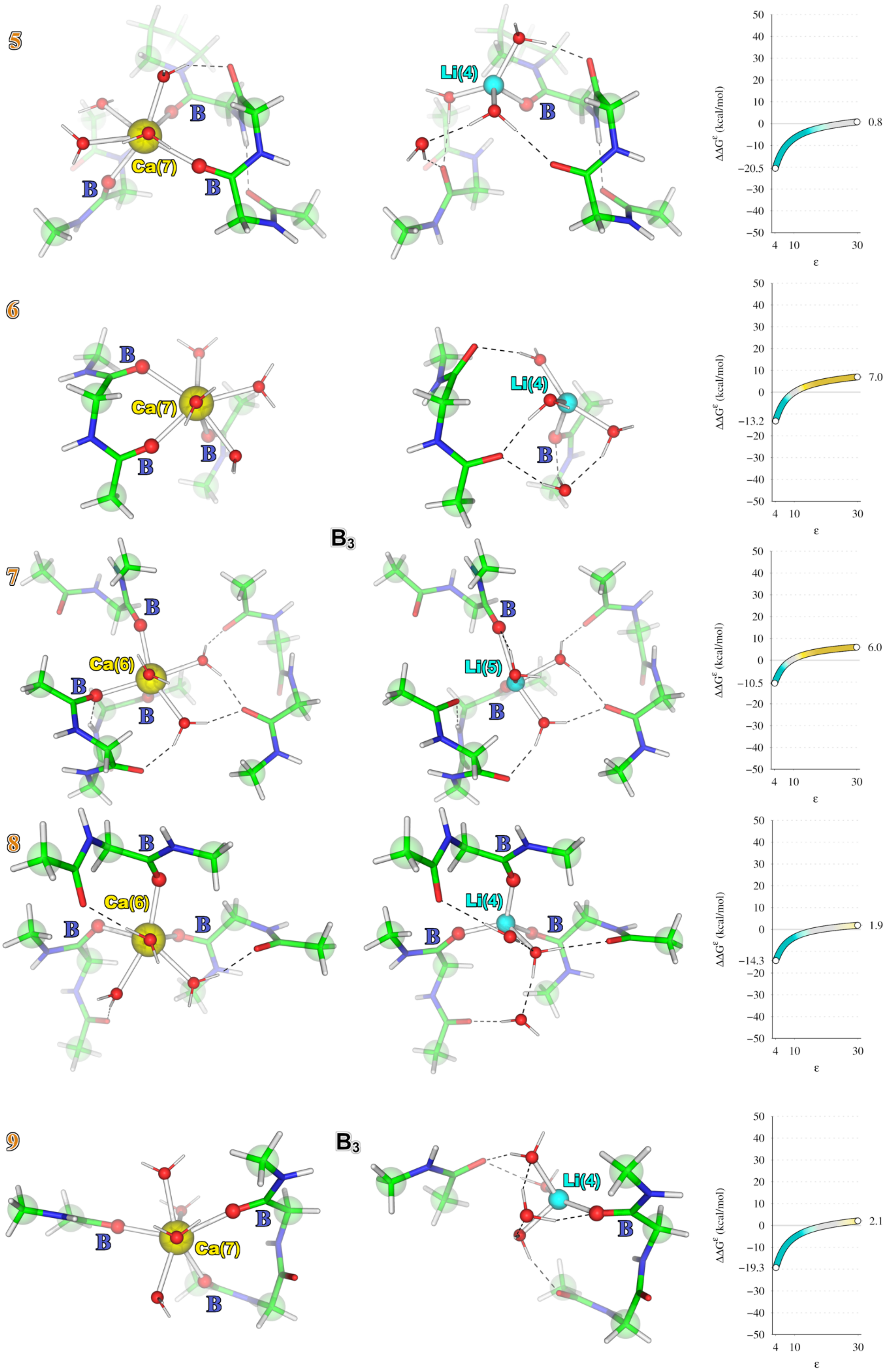



5
Ca(7)
Li(6)
B
6
Ca(7)
Li(5)
B
B2
7
Ca(7)
Li(4)
B
8
Ca(7)
Li(5)
B
ΔΔG^ε (kcal/mol)
ε
3.4
−16.7
5.2
−14.6
2.3
−18.7
1.0
−20.2
50
40
30
20
10
0
−10
−20
−30
−40
−50
4
10
30


9
B
B
Ca(7)
B
Li(4)
ΔΔG^ε (kcal/mol)
4.2
−17.6
ε
B2
10
B
B
Ca(7)
Li(4)
ΔΔG^ε (kcal/mol)
6.0
−13.8
ε

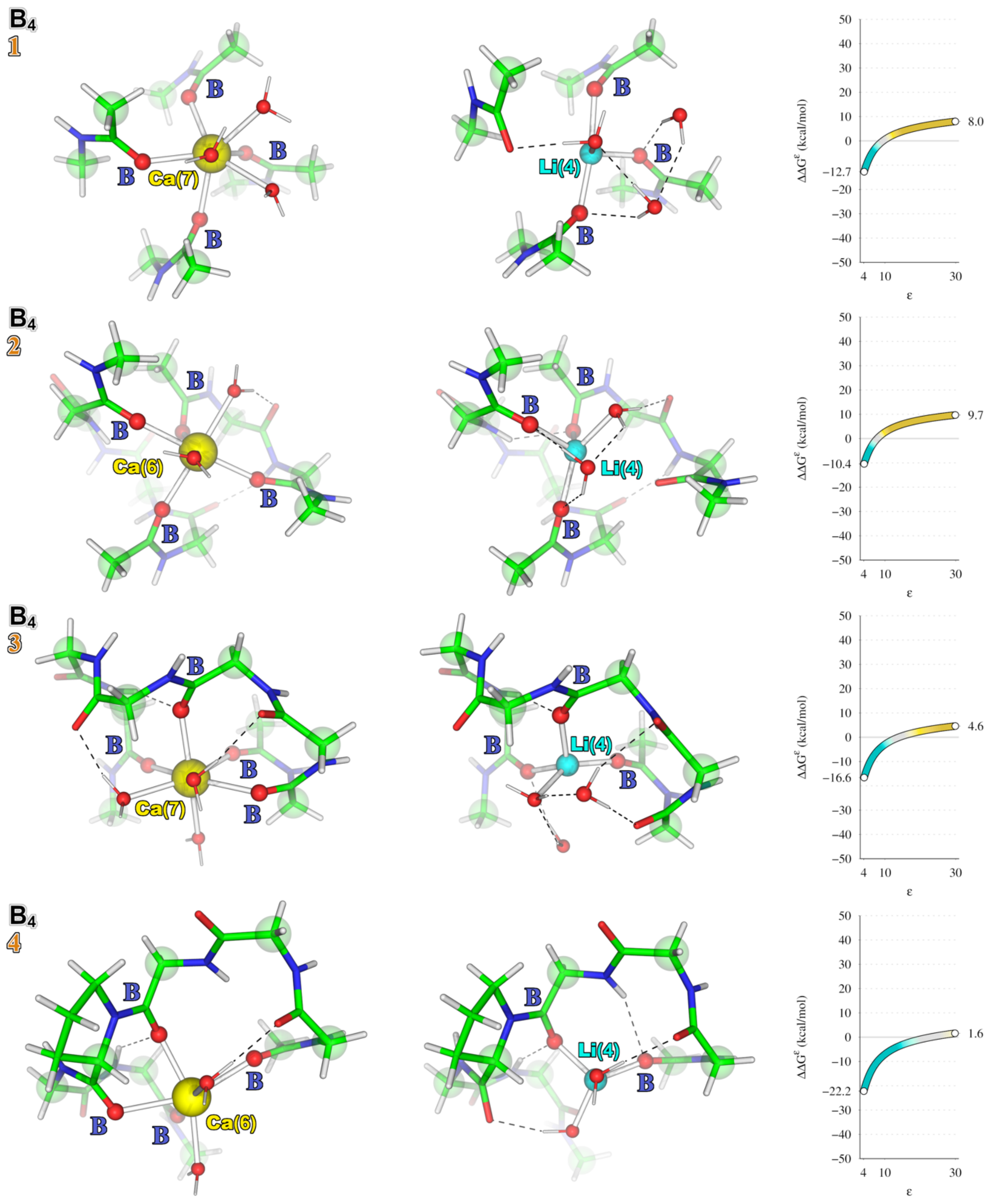
Supporting Information Figure S1b. Models for B_3 Ca^{2+}-sites containing three backbone ligands.

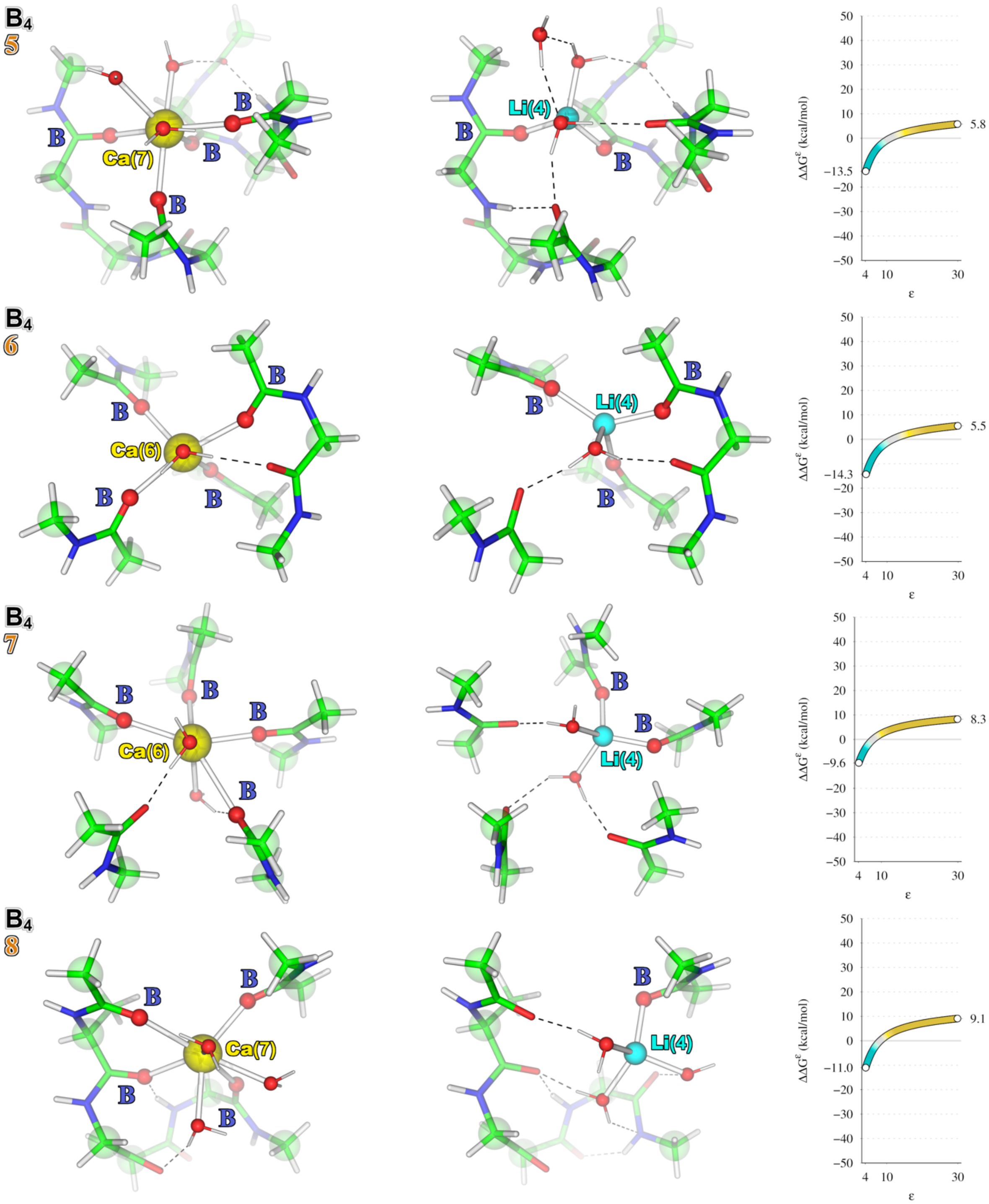


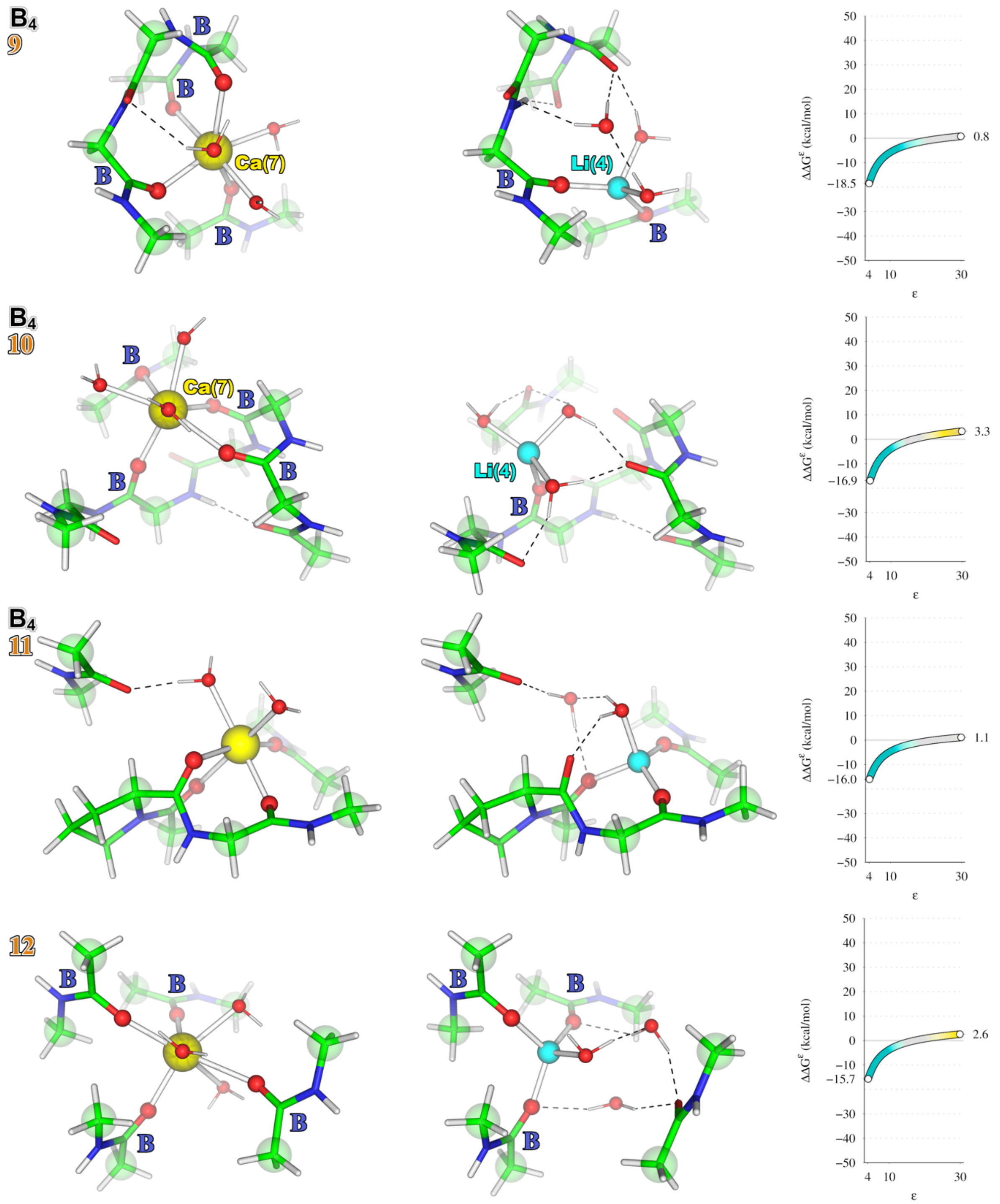


5
Ca(7)
Li(4)
B
0.8
−20.5
6
Ca(7)
Li(4)
7.0
−13.2
B3
7
Ca(6)
Li(5)
6.0
−10.5
8
Ca(6)
Li(4)
1.9
−14.3
9
B3
Ca(7)
Li(4)
2.1
−19.3
ΔΔG^ε (kcal/mol)
ε
50
40
30
20
10
0
−10
−20
−30
−40
−50
4
10
30

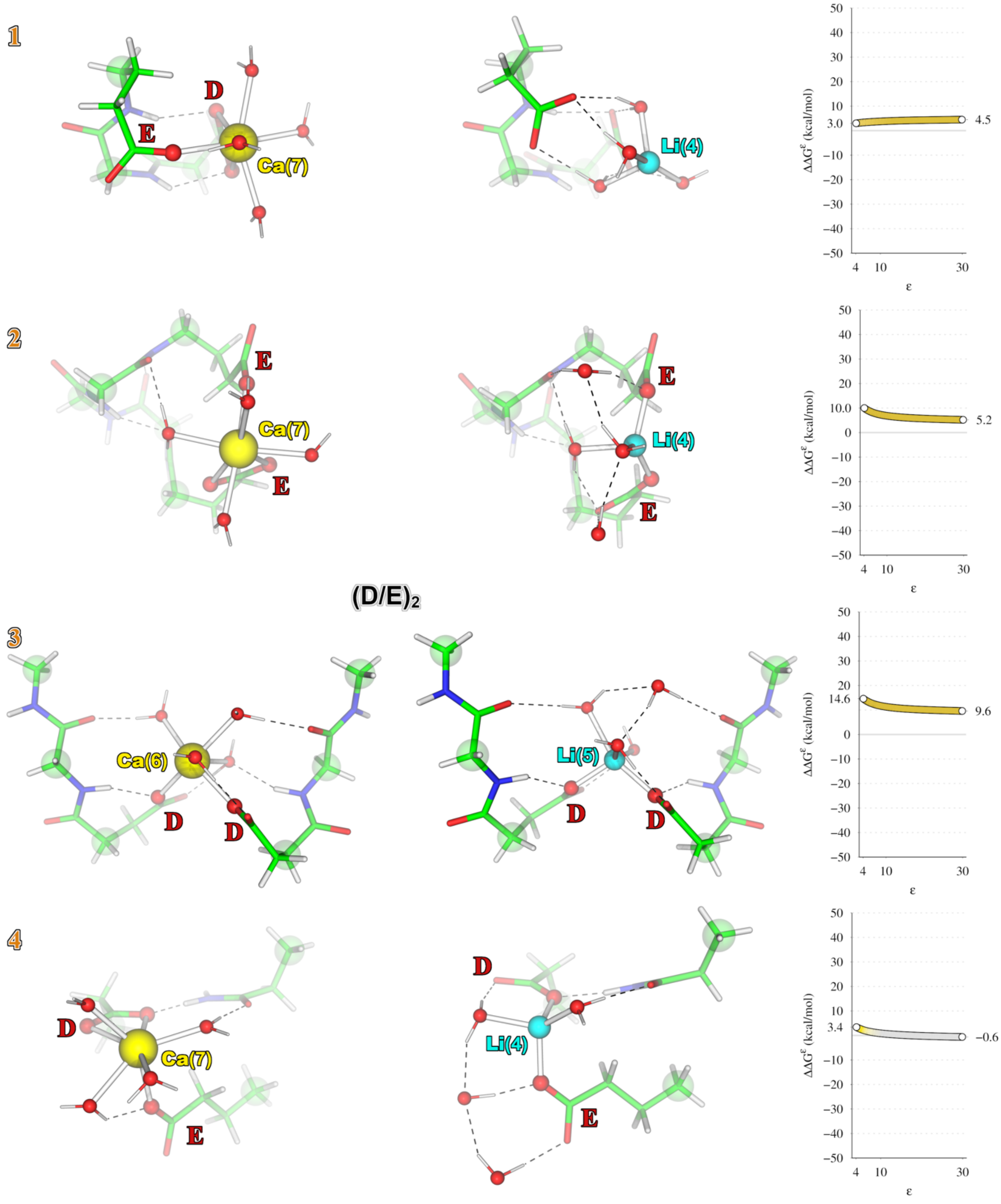
Supporting Information Figure S1c. Models for $B_4\,Ca^{2+}$-sites containing four backbone ligands.

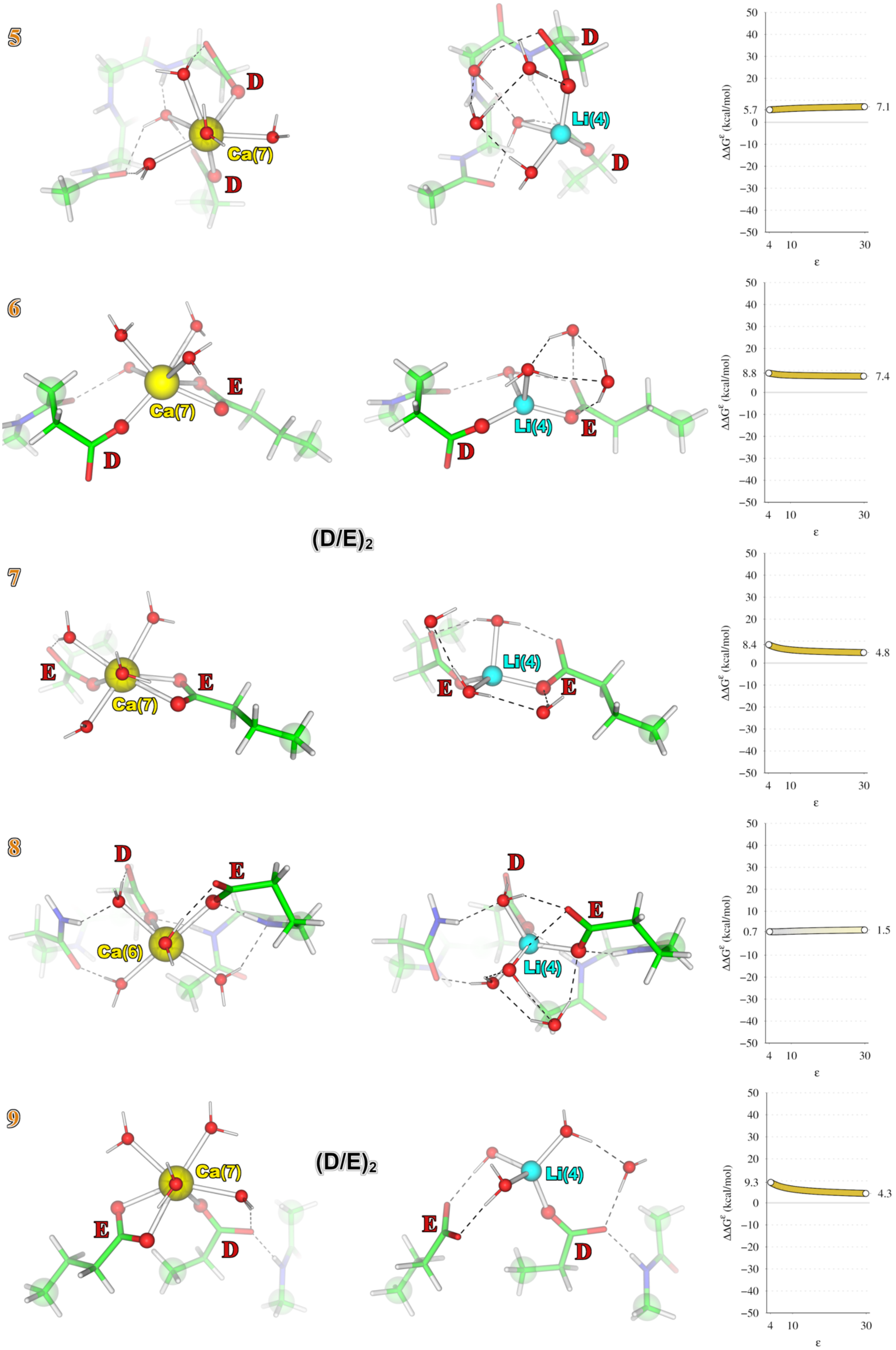



B4
5
Ca(7)
Li(4)
ΔΔG^ε (kcal/mol)
ε
5.8
-13.5
B4
6
Ca(6)
Li(4)
5.5
-14.3
B4
7
Ca(6)
Li(4)
8.3
-9.6
B4
8
Ca(7)
Li(4)
9.1
-11.0


B4
9
B
Ca(7)
Li(4)
0.8
−18.5
B4
10
3.3
−16.9
B4
11
1.1
−16.0
12
2.6
−15.7
ΔΔG^ε (kcal/mol)
ε
50
40
30
20
10
0
−10
−30
−40
−50
4
10
30

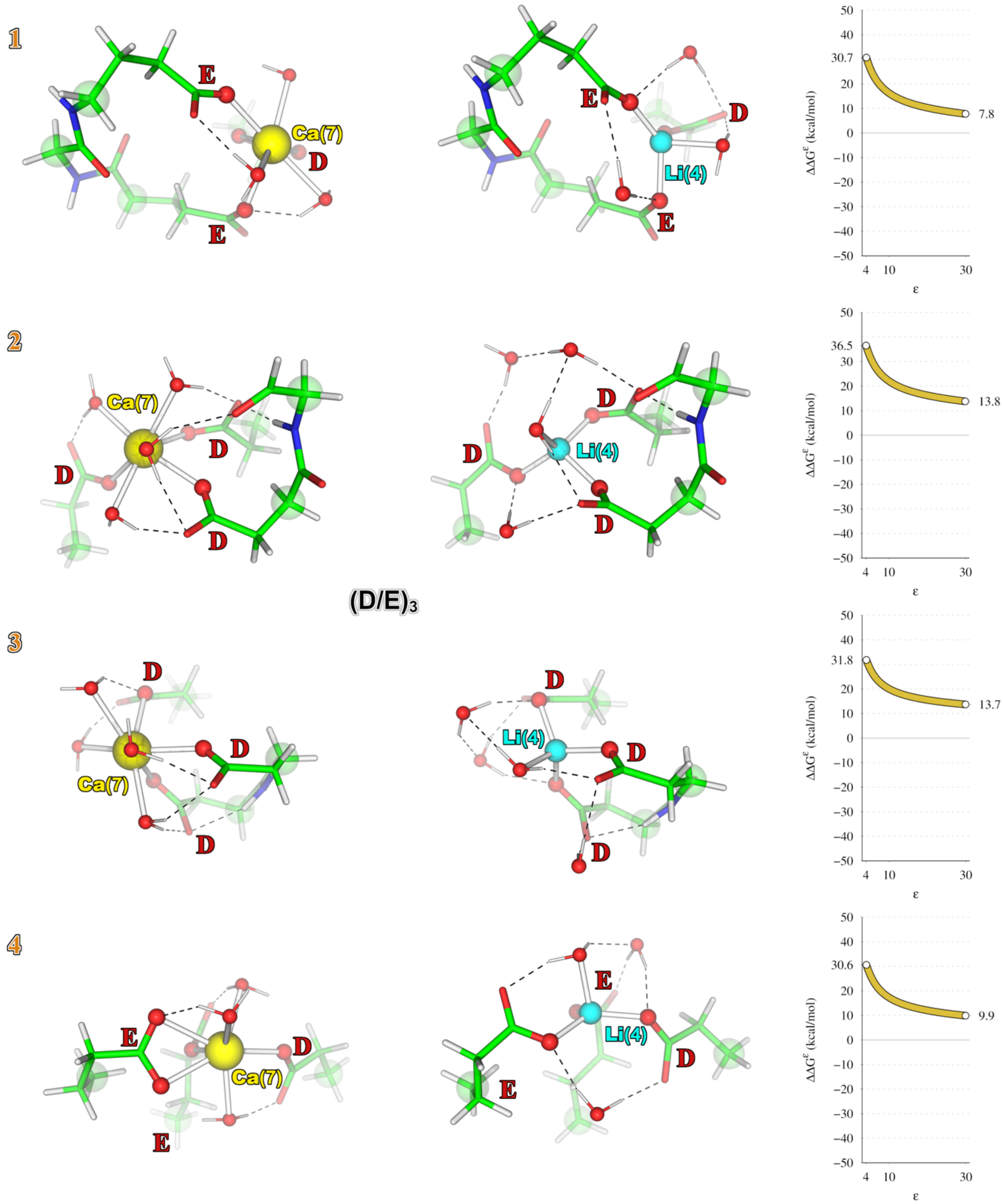
Supporting Information Figure S1d. Models for $(D/E)_2\ Ca^{2+}$-sites containing two carboxylate ligands.

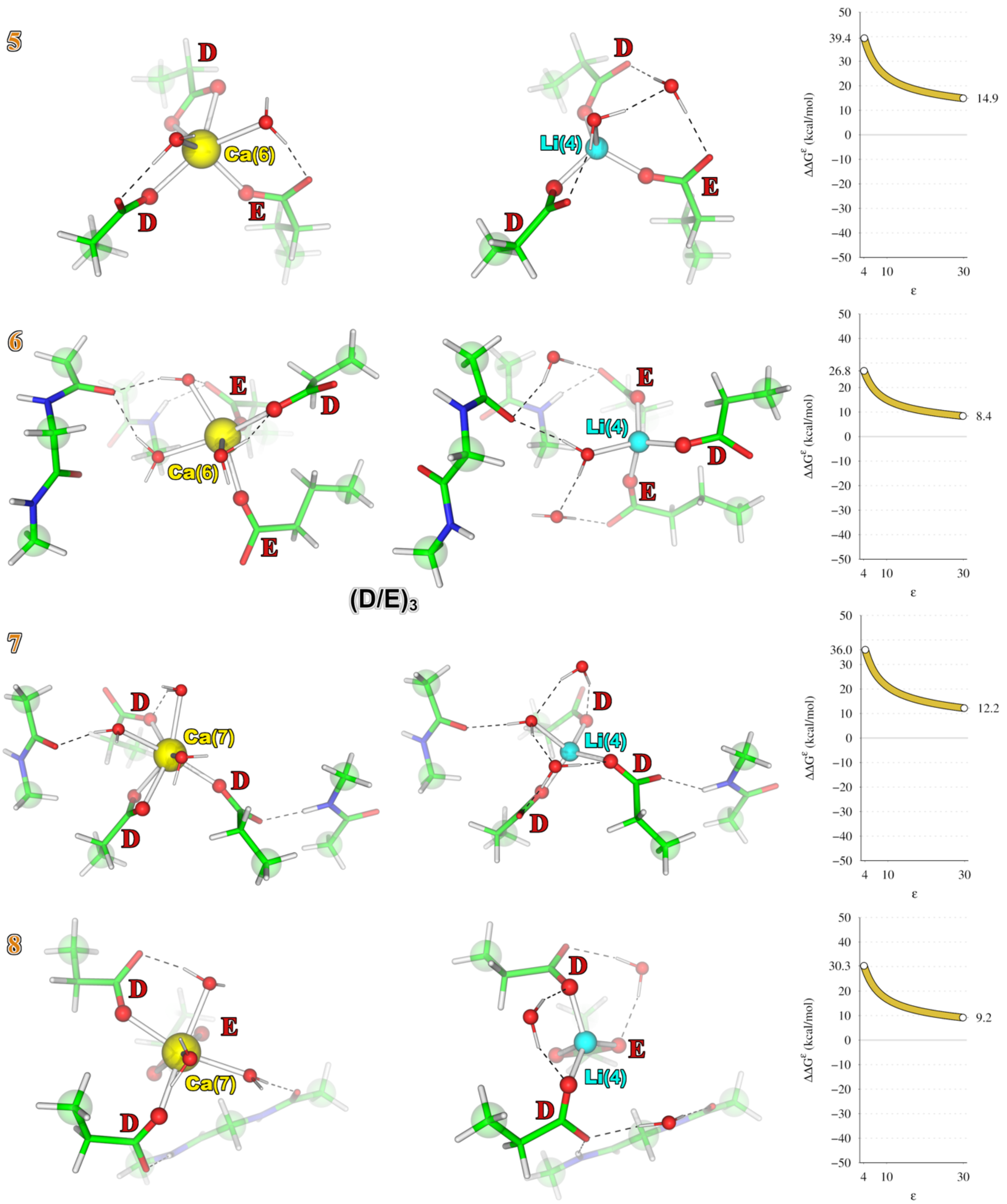


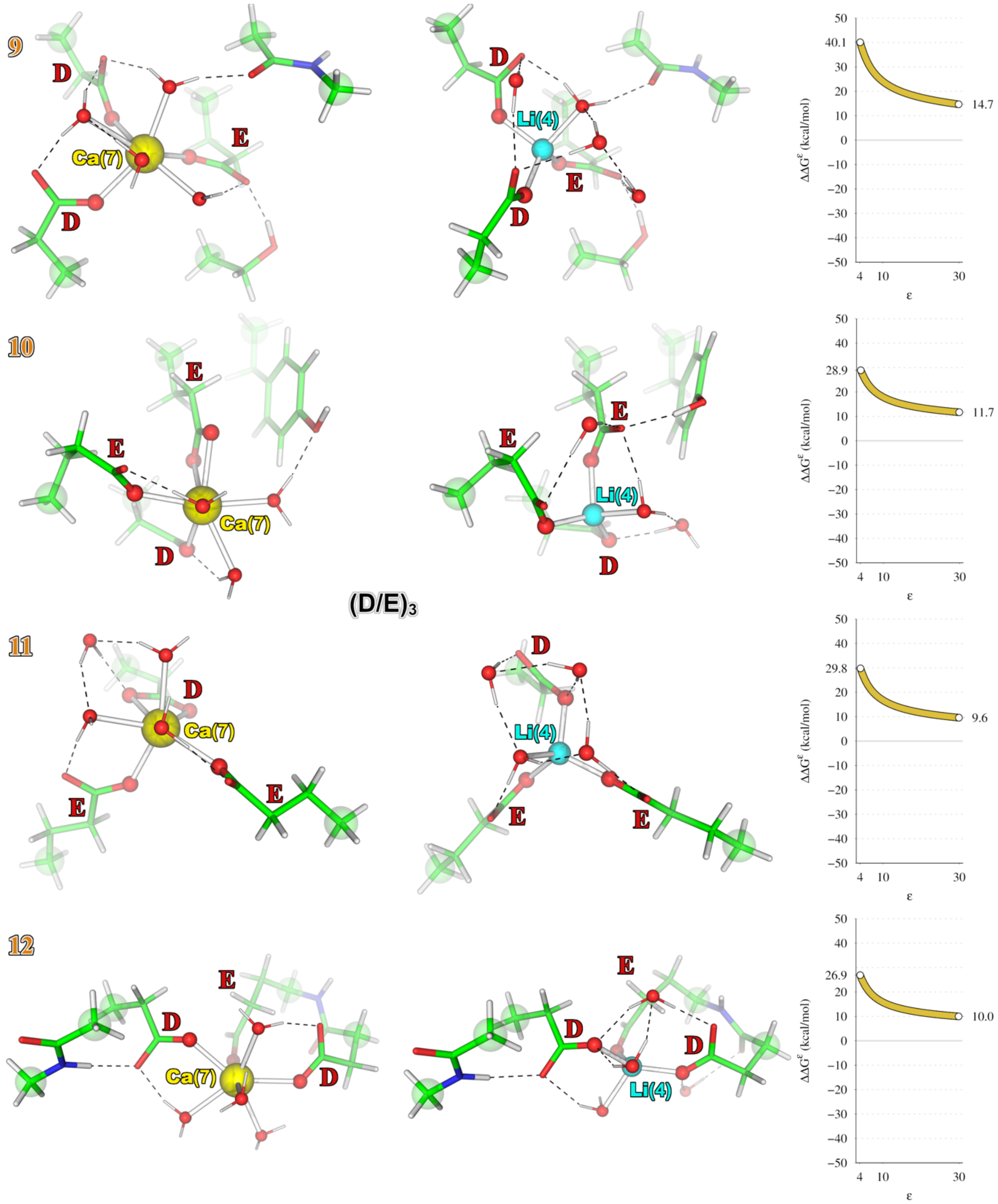


5
D
Ca(7)
D
D
Li(4)
D
ΔΔG^ε (kcal/mol)
5.7
7.1
ε
6
Ca(7)
E
D
Li(4)
E
D
ΔΔG^ε (kcal/mol)
8.8
7.4
ε
(D/E)2
7
E
E
Ca(7)
Li(4)
E
E
ΔΔG^ε (kcal/mol)
8.4
4.8
ε
8
D
E
Ca(6)
D
E
Li(4)
ΔΔG^ε (kcal/mol)
0.7
1.5
ε
9
Ca(7)
(D/E)2
E
D
Li(4)
E
D
ΔΔG^ε (kcal/mol)
9.3
4.3
ε

Supporting Information Figure S1e. Models for $(D/E)_3$ Ca^{2+}-sites containing three carboxylate ligands.

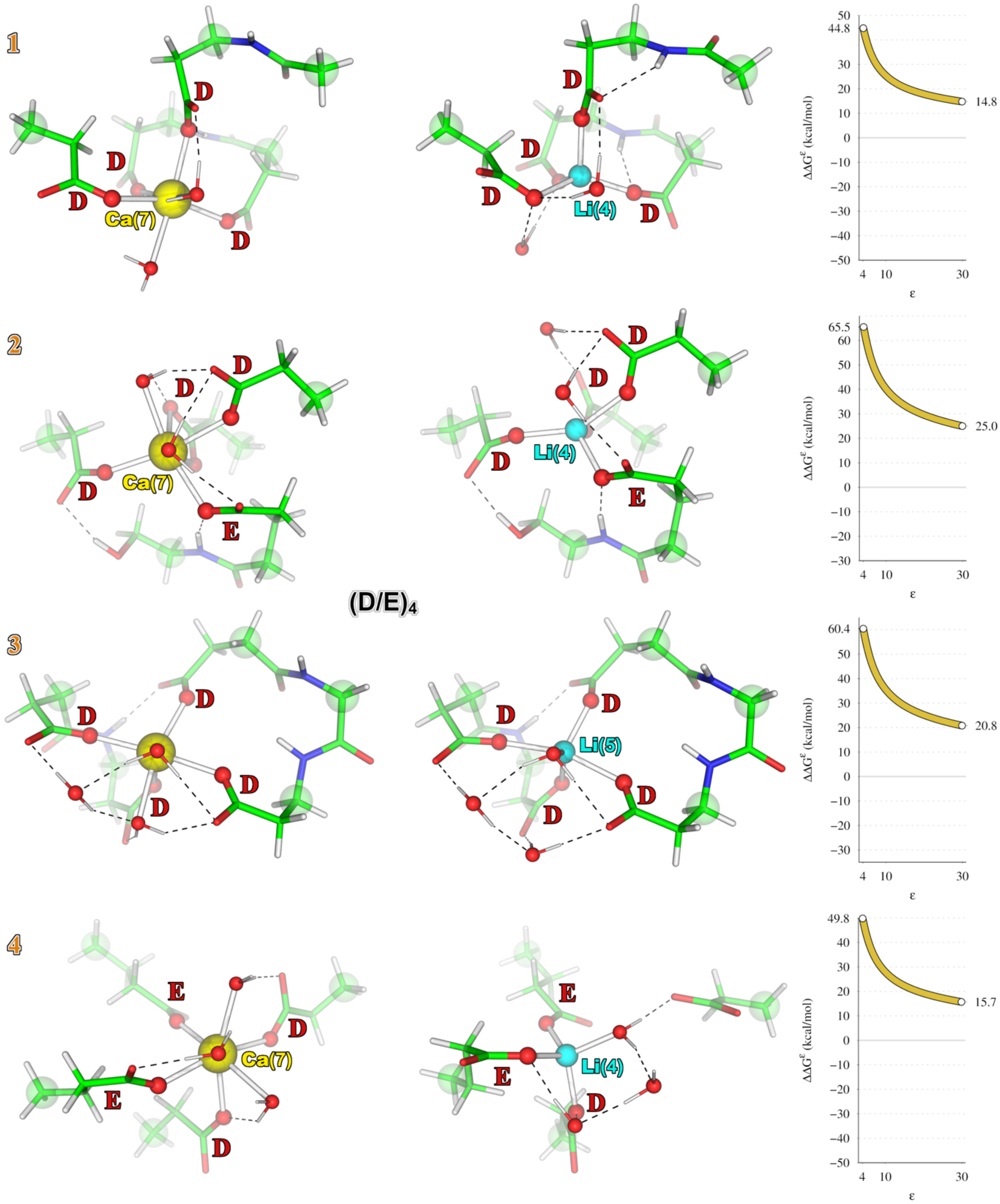


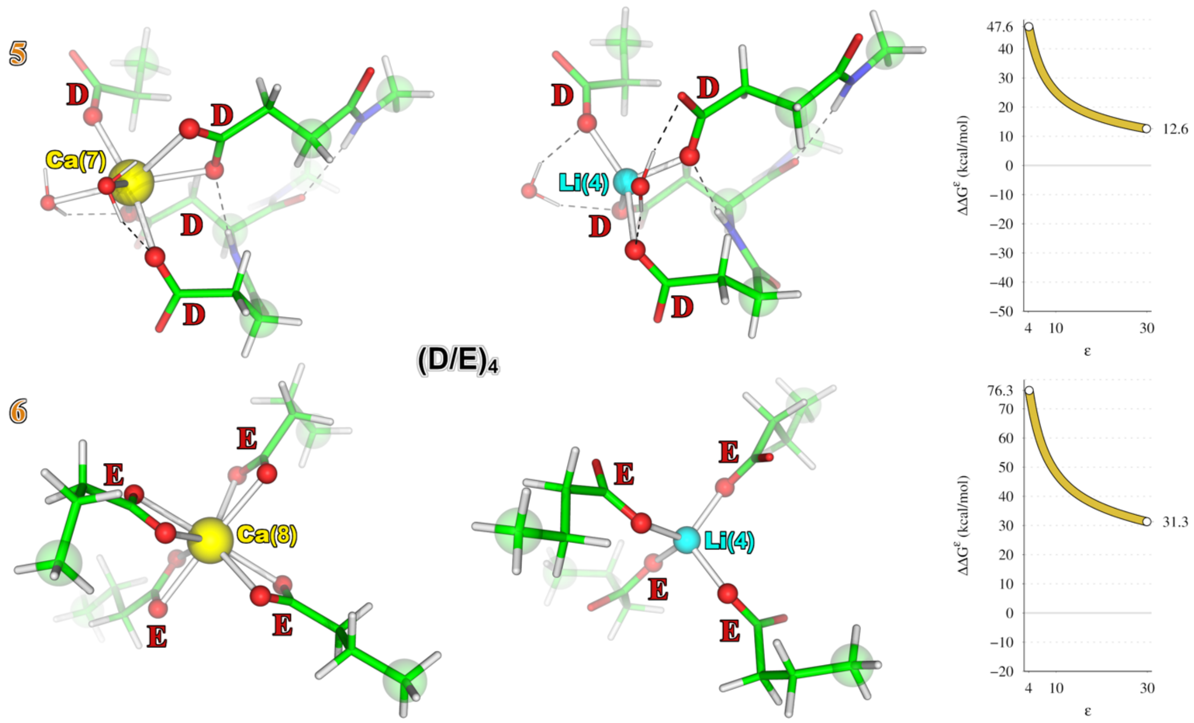

5
D
Ca(6)
D
E
D
Li(4)
E
D
ΔΔG^ε (kcal/mol)
39.4
14.9
ε
6
E
D
Ca(6)
E
E
Li(4)
D
E
26.8
8.4
(D/E)3
7
D
Ca(7)
D
D
D
Li(4)
D
D
36.0
12.2
8
D
E
Ca(7)
D
D
E
Li(4)
D
30.3
9.2



(D/E)3
9
10
11
12
Ca(7)
Li(4)
D
E
ΔΔG^ε (kcal/mol)
ε
40.1
14.7
28.9
11.7
29.8
9.6
26.9
10.0

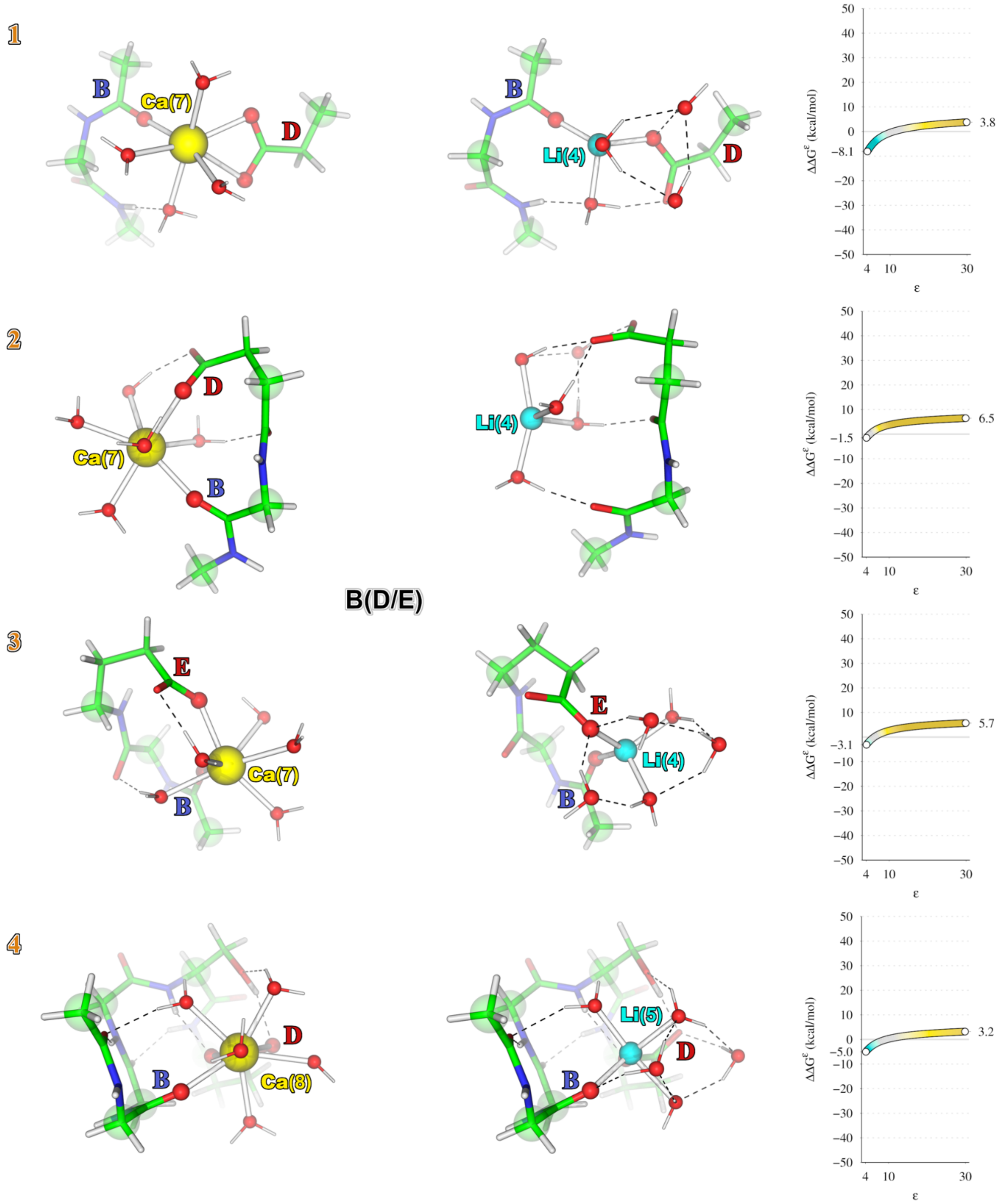
Supporting Information Figure S1f. Models for (D/E)$_4$ Ca^{2+}-sites containing four carboxylate ligands.



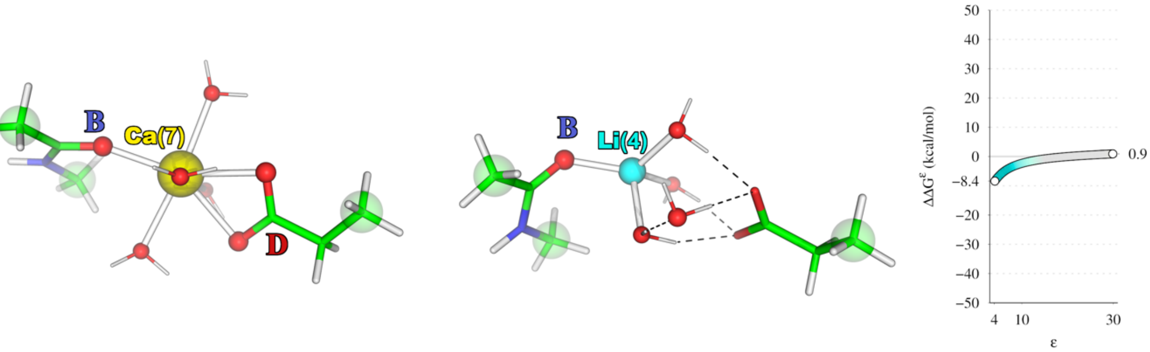


5
D
Ca(7)
Li(4)
(D/E)4
6
E
Ca(8)
Li(4)
ΔΔG^ε (kcal/mol)
ε
47.6
12.6
76.3
31.3

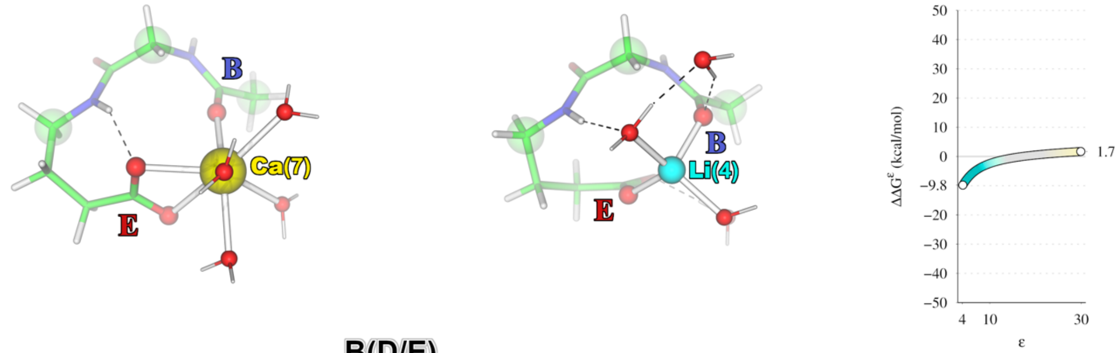
Supporting Information Figure S1g. Models for B(D/E) Ca^{2+}-sites containing a backbone ligand and a carboxylate ligand.



5

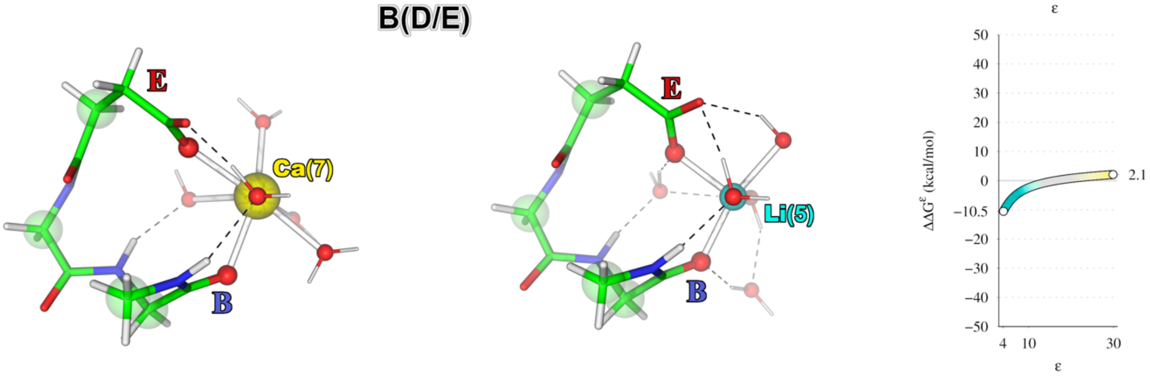

B
Ca(7)
D
B
Li(4)
50
40
30
20
10
0
−8.4
−20
−30
−40
−50
ΔΔG$^{\varepsilon}$ (kcal/mol)
0.9
4
10
30
ε

6

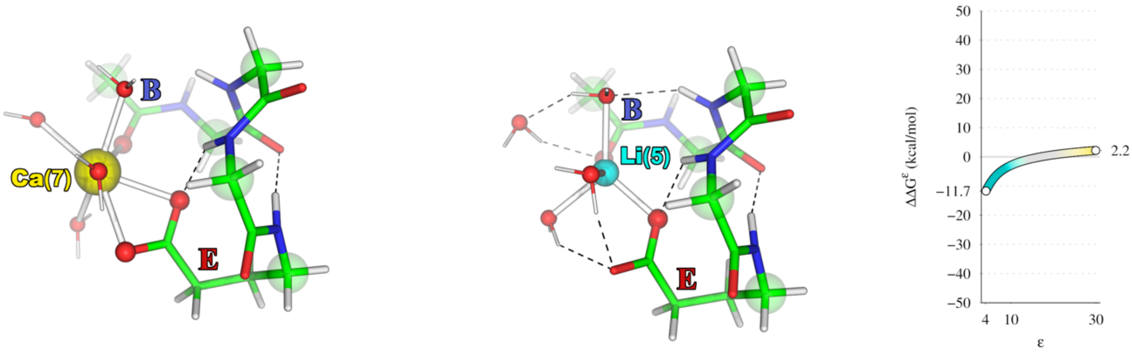

B
Ca(7)
E
B
Li(4)
E
50
40
30
20
10
0
−9.8
−20
−30
−40
−50
ΔΔG$^{\varepsilon}$ (kcal/mol)
1.7
4
10
30
ε

B(D/E)

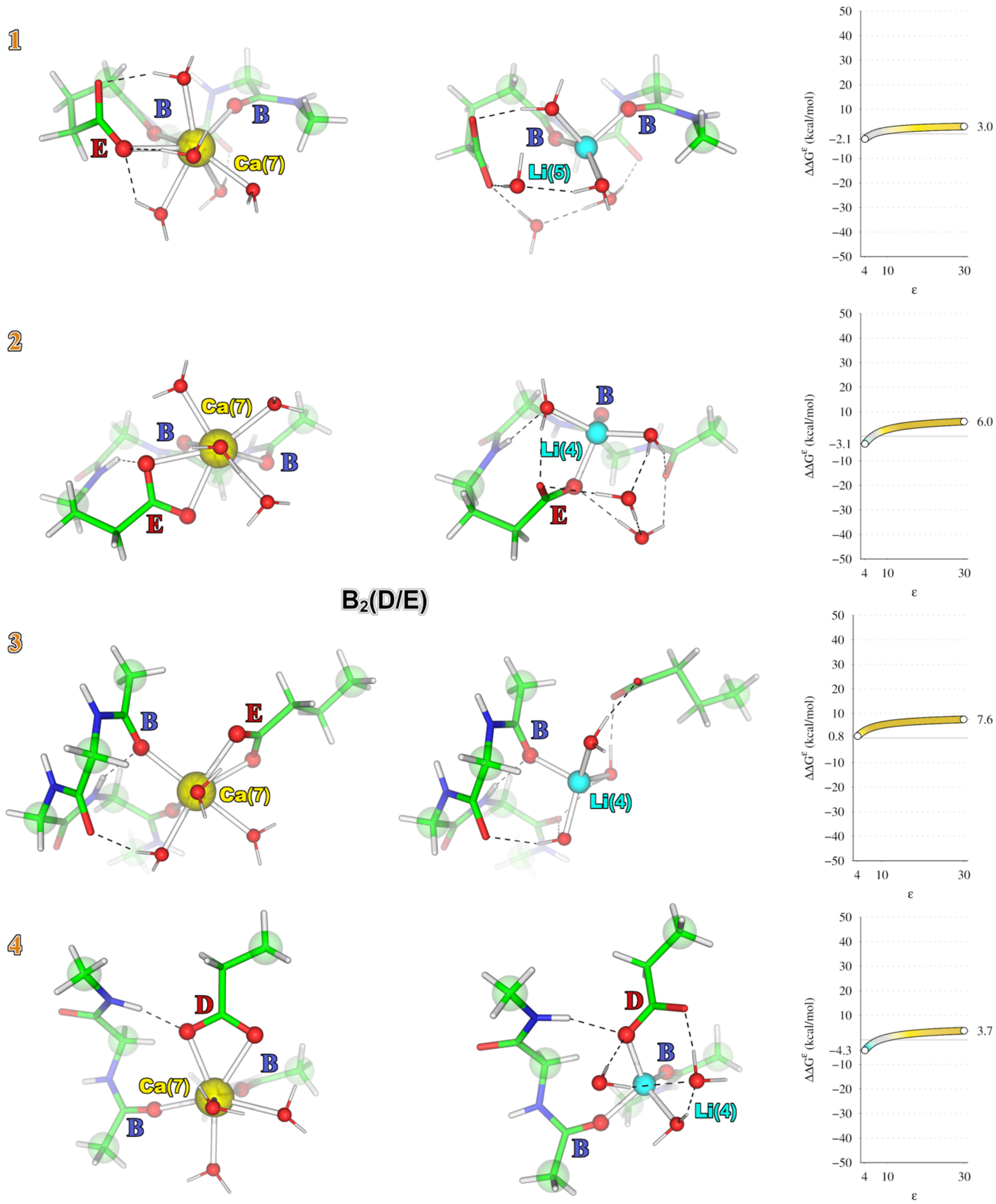
7

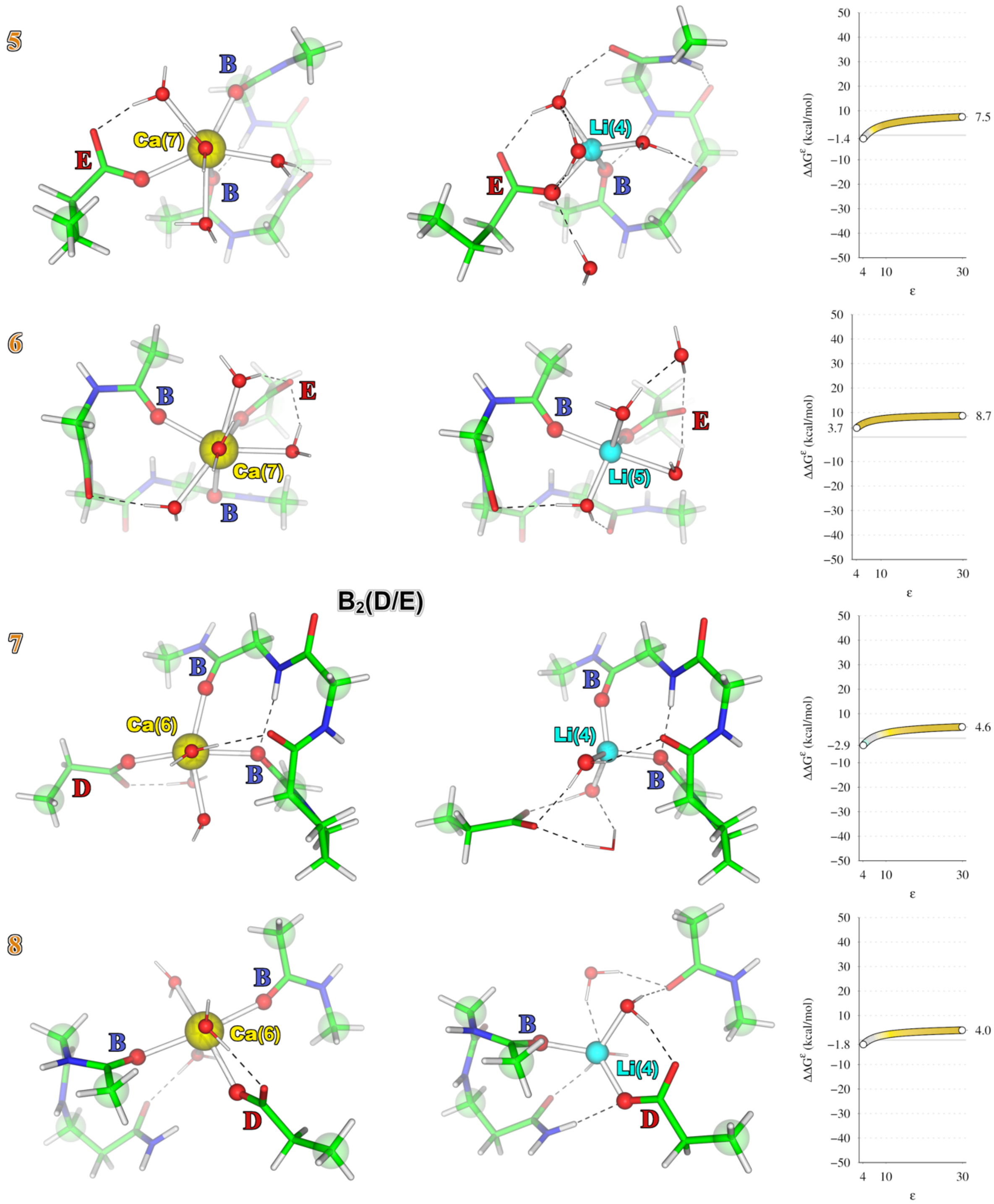

E
Ca(7)
B
E
Li(5)
B
50
40
30
20
10
0
−10.5
−20
−30
−40
−50
ΔΔG$^{\varepsilon}$ (kcal/mol)
2.1
4
10
30
ε

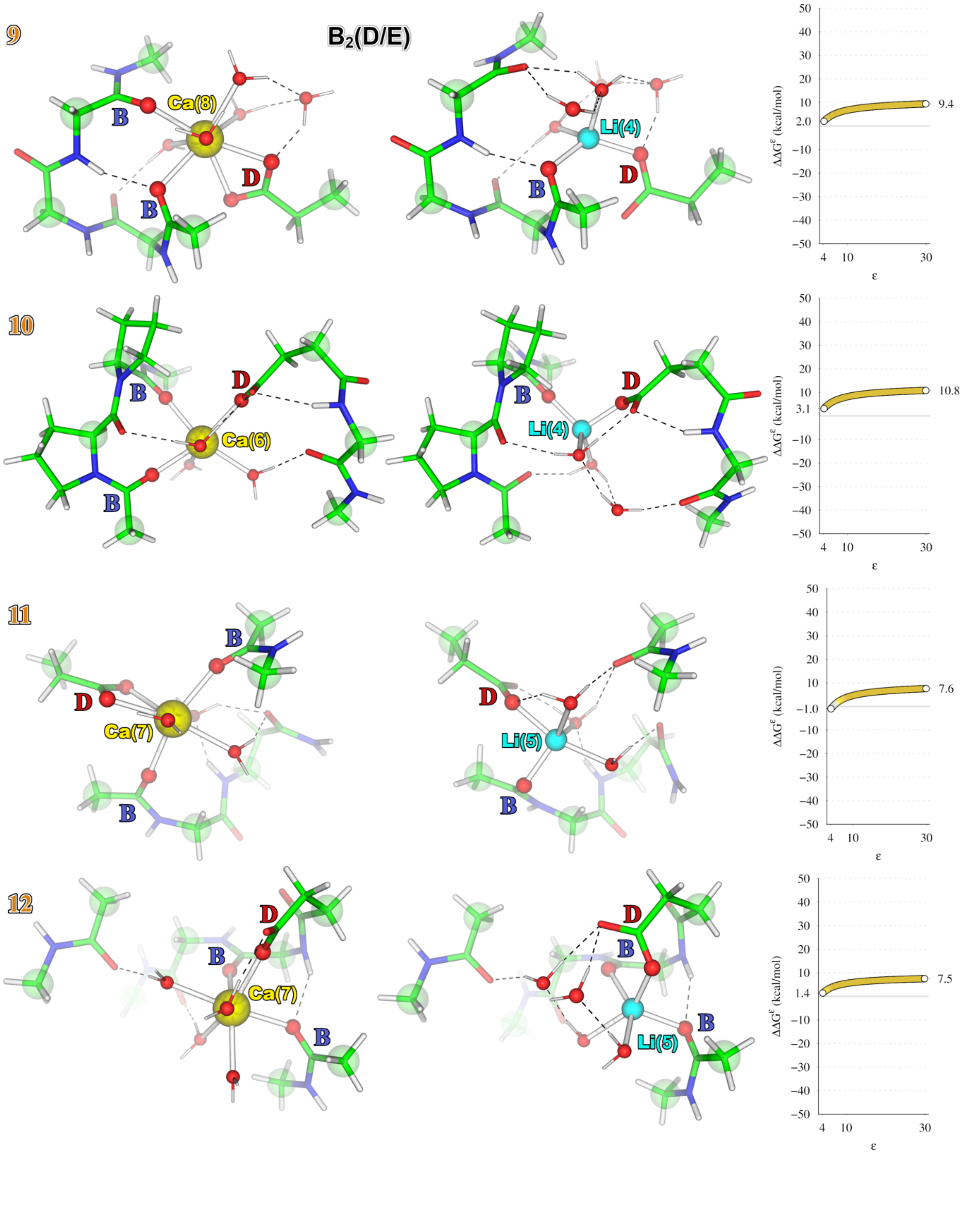
8


B
Ca(7)
E
B
Li(5)
E
50
40
30
20
10
0
−11.7
−20
−30
−40
−50
ΔΔG$^{\varepsilon}$ (kcal/mol)
2.2
4
10
30
ε

Supporting Information Figure S1h. Models for B_2(D/E) Ca^{2+}-sites containing two backbone ligands and a carboxylate ligand.

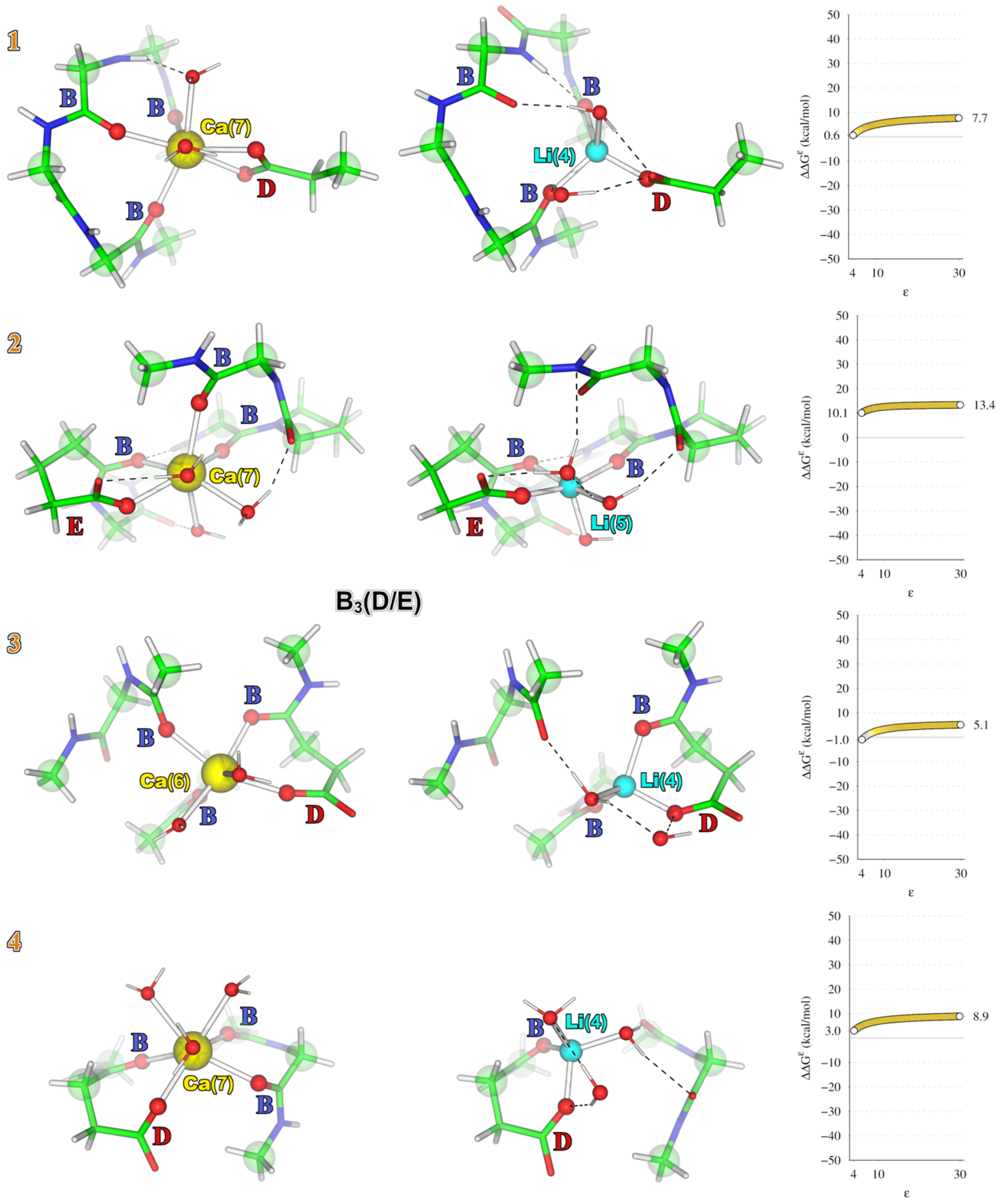


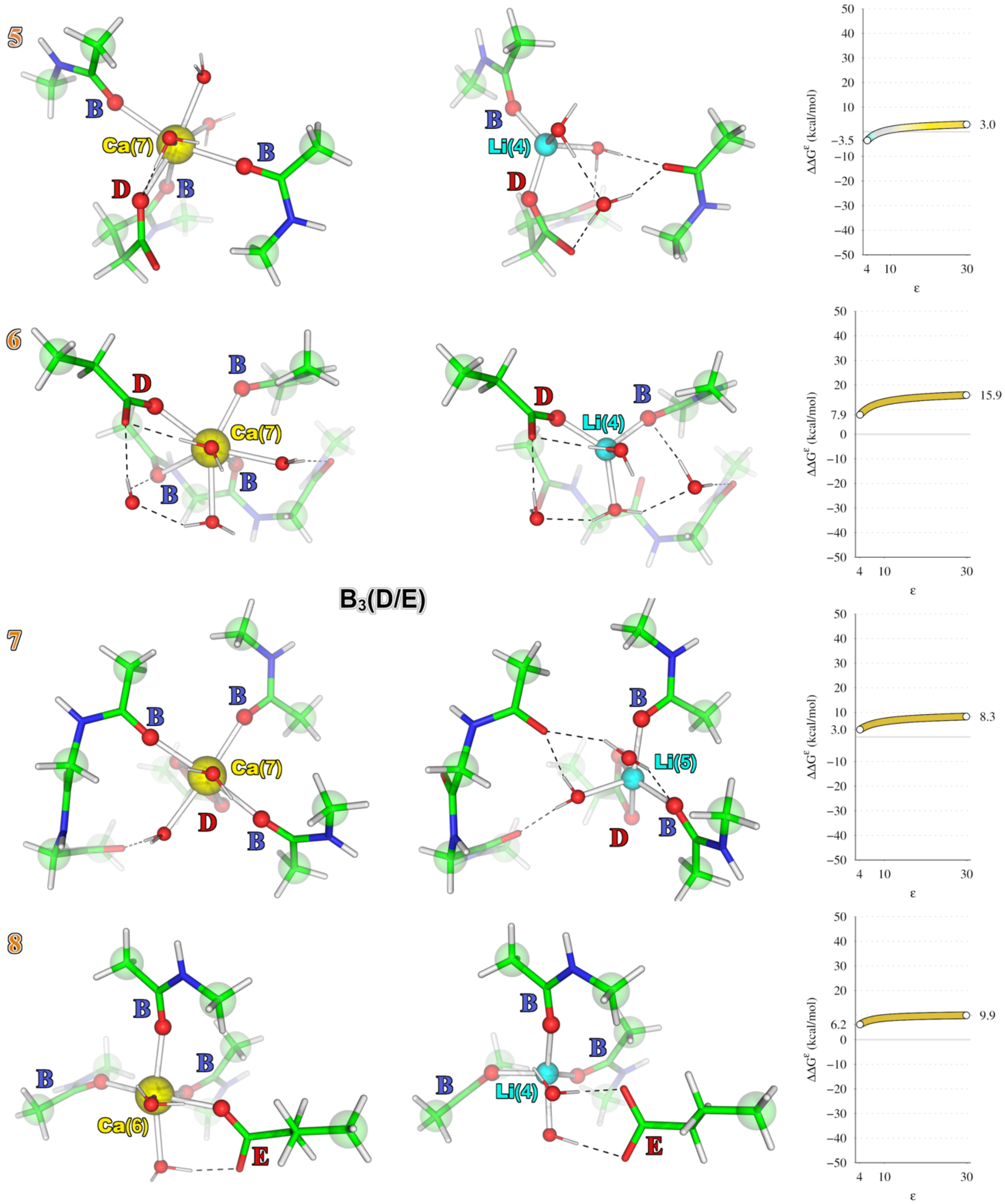

5
B
Ca(7)
E
B
Li(4)
E
B
7.5
-1.4
ΔΔG^ε (kcal/mol)
ε
6
B
E
Ca(7)
B
B
Li(5)
E
8.7
3.7
ΔΔG^ε (kcal/mol)
ε
B₂(D/E)
7
B
Ca(6)
D
B
B
Li(4)
B
4.6
-2.9
ΔΔG^ε (kcal/mol)
ε
8
B
B
Ca(6)
D
B
Li(4)
D
4.0
-1.8
ΔΔG^ε (kcal/mol)
ε



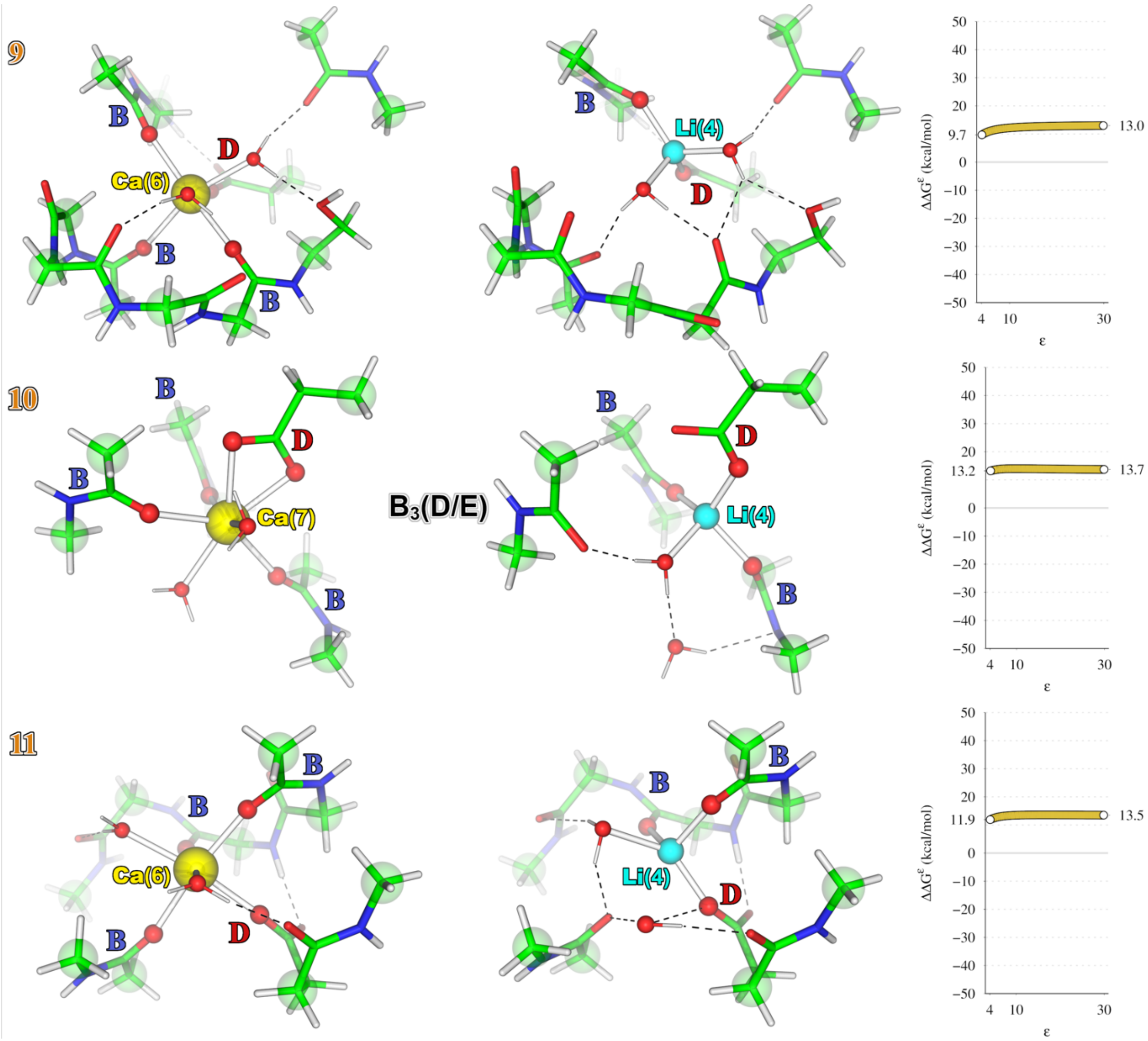
B2(D/E)
9
Ca(8)
Li(4)
B
B
D
ΔΔGε (kcal/mol)
ε
9.4
2.0
10
Ca(6)
Li(4)
B
B
D
10.8
3.1
11
Ca(7)
Li(5)
B
B
D
7.6
-1.0
12
Ca(7)
Li(5)
B
B
D
7.5
1.4

Supporting Information Figure S1i. Models for B_3(D/E) Ca^{2+}-sites containing three backbone ligands and a carboxylate ligand.

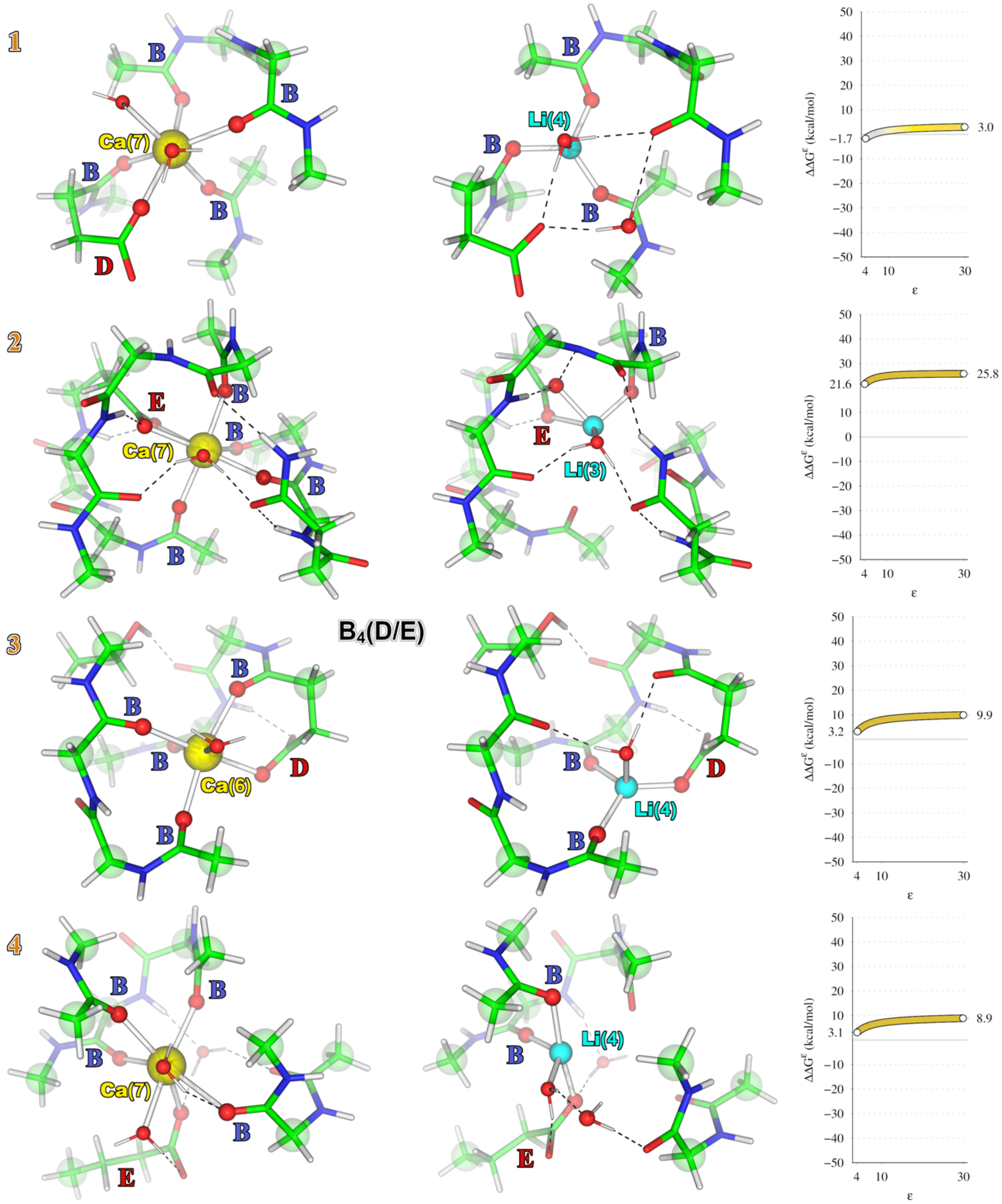


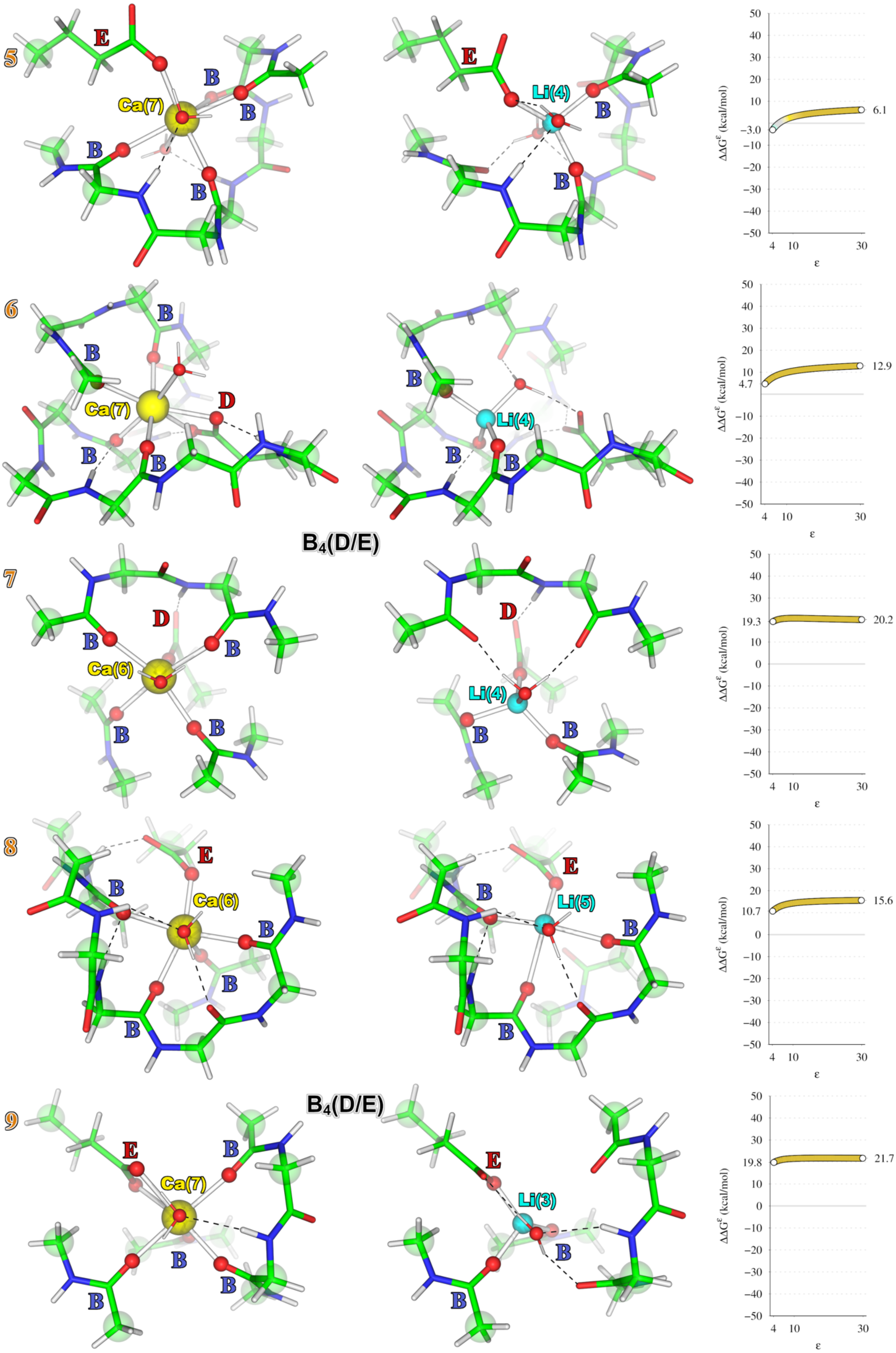


5
B
Ca(7)
B
D
B
B
Li(4)
D
ΔΔG^ε (kcal/mol)
−3.5
3.0
ε
6
D
B
Ca(7)
B
B
D
Li(4)
B
ΔΔG^ε (kcal/mol)
7.9
15.9
ε
B3(D/E)
7
B
B
Ca(7)
D
B
B
Li(5)
D
B
ΔΔG^ε (kcal/mol)
3.0
8.3
ε
8
B
B
B
Ca(6)
E
B
B
B
Li(4)
E
ΔΔG^ε (kcal/mol)
6.2
9.9
ε

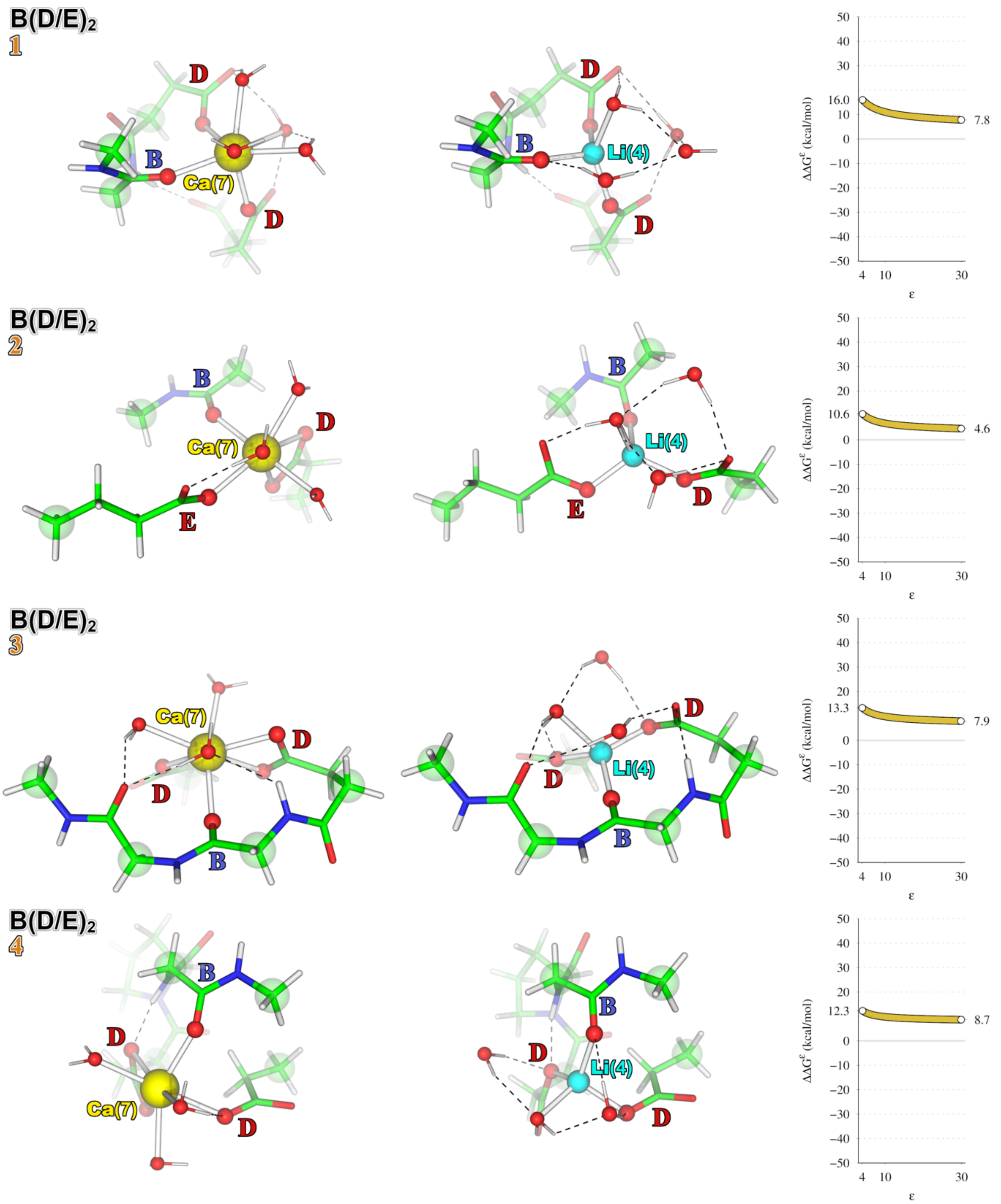

9
B
D
Ca(6)
B
B
B
Li(4)
D
10
B
B
D
Ca(7)
B
B_3(D/E)
B
D
Li(4)
B
11
B
B
Ca(6)
D
B
B
B
Li(4)
D
ΔΔG^{ε} (kcal/mol)
ε
9.7
13.0
13.2
13.7
11.9
13.5

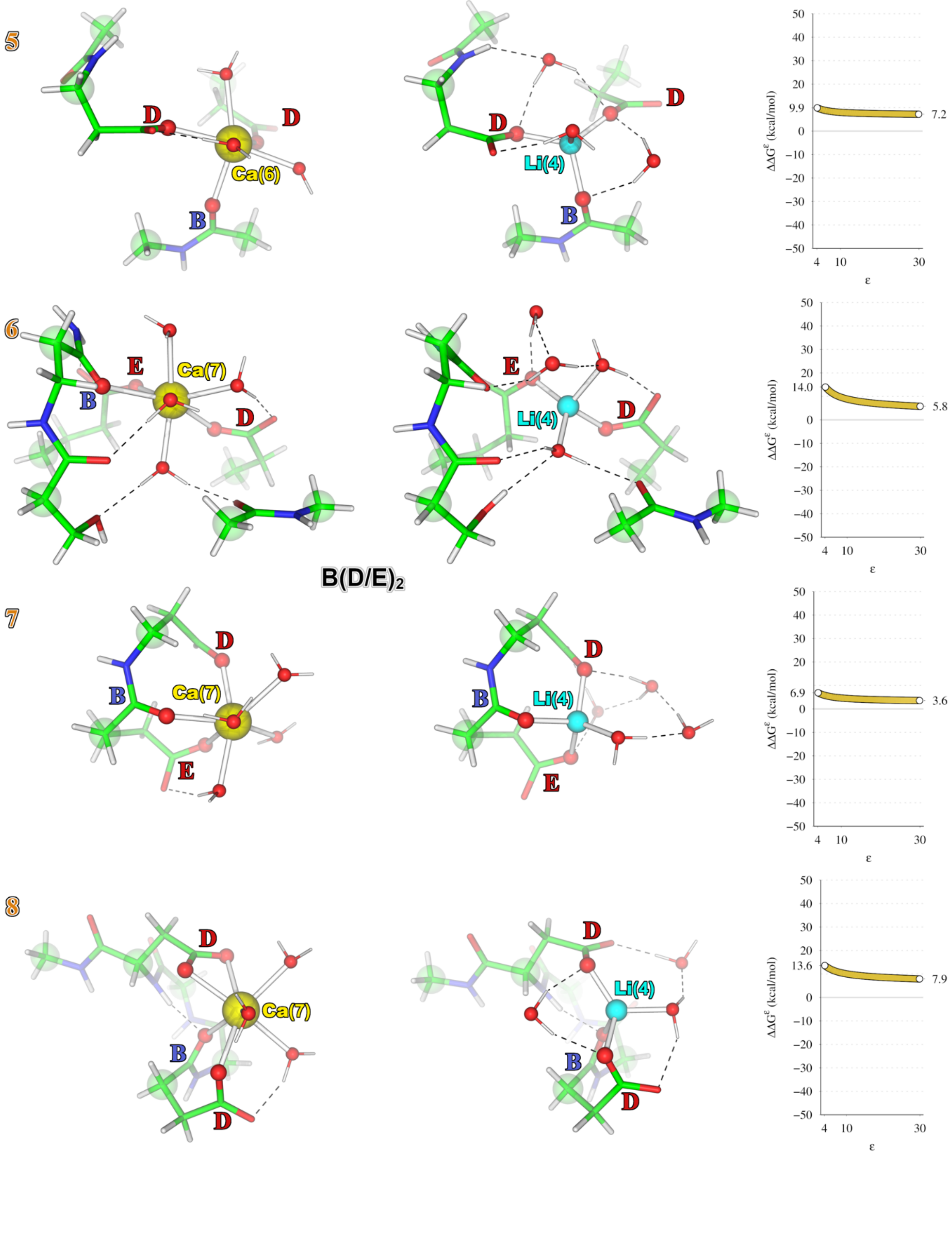
Supporting Information Figure S1j. Models for B4(D/E) Ca^{2+}-sites containing four backbone ligands and a carboxylate ligand.




5
E
B
B
B
B
Ca(7)
Li(4)
6.1
−3.0
ΔΔG^ε (kcal/mol)
ε
6
Ca(7)
D
Li(4)
12.9
4.7
B4(D/E)
7
Ca(6)
Li(4)
19.3
20.2
8
Ca(6)
Li(5)
10.7
15.6
B4(D/E)
9
Ca(7)
Li(3)
19.8
21.7

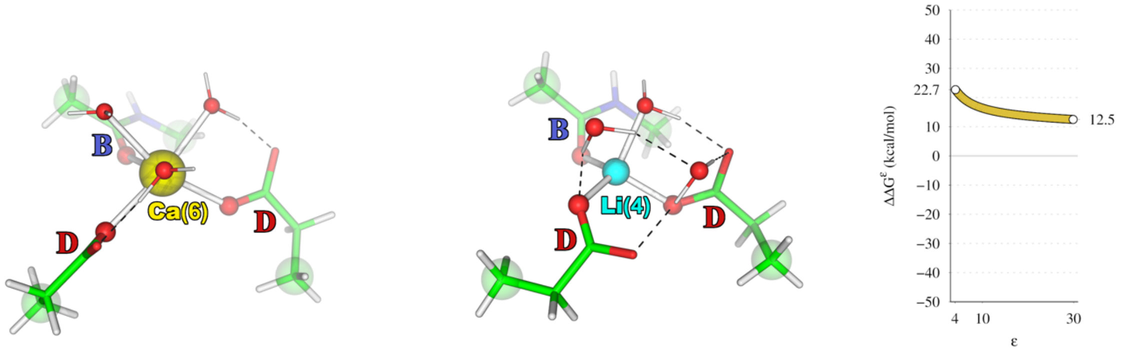
Supporting Information Figure S1k. Models for B(D/E)$_2$ Ca^{2+}-sites containing a backbone ligand and two carboxylate ligands.



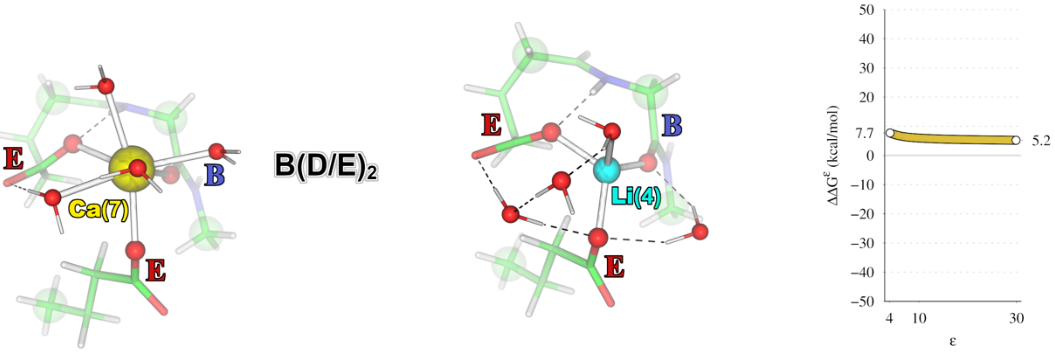


5
D
D
Ca(6)
B
D
D
Li(4)
B
9.9
7.2
6
E
Ca(7)
B
D
E
Li(4)
D
14.0
5.8
B(D/E)2
7
D
B
Ca(7)
E
D
B
Li(4)
E
6.9
3.6
8
D
Ca(7)
B
D
D
Li(4)
B
D
13.6
7.9
ΔΔG^ε (kcal/mol)
ε

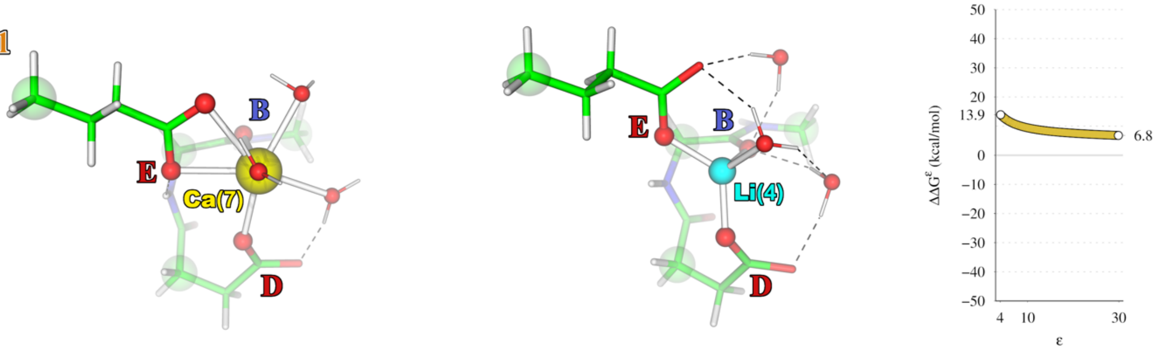
9


B
D
Ca(6)
Li(4)
ΔΔG^ε (kcal/mol)
22.7
12.5
ε

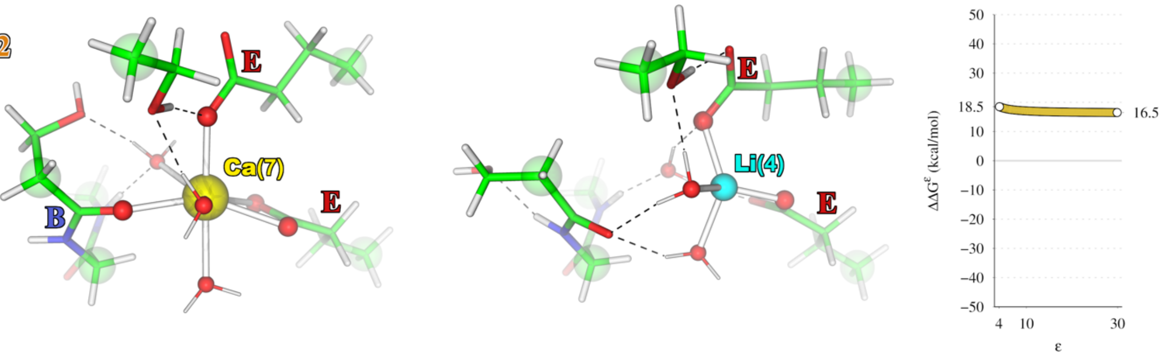
10


E
B
Ca(7)
B(D/E)2
Li(4)
ΔΔG^ε (kcal/mol)
7.7
5.2
ε

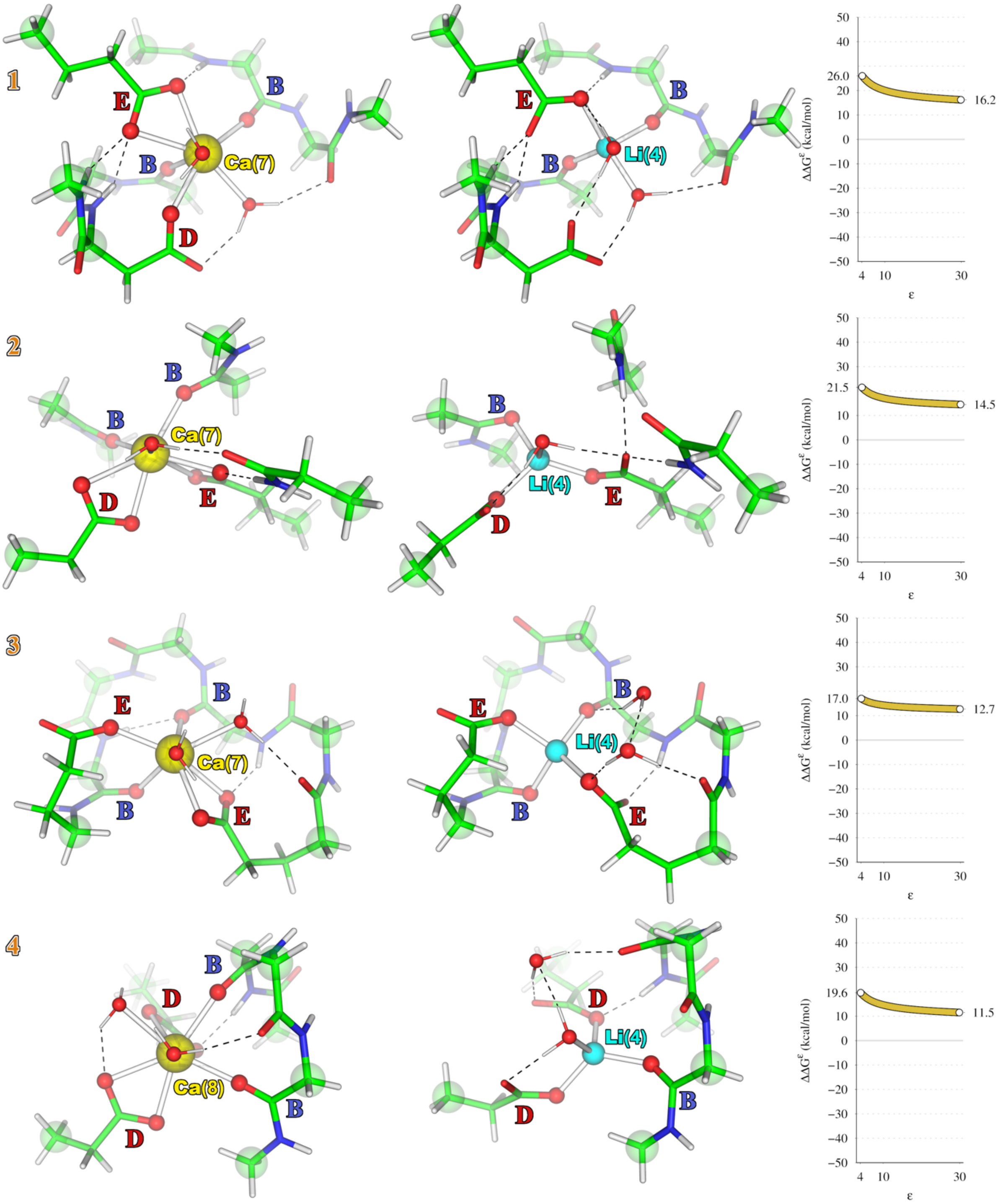
11


E
B
D
Ca(7)
Li(4)
ΔΔG^ε (kcal/mol)
13.9
6.8
ε

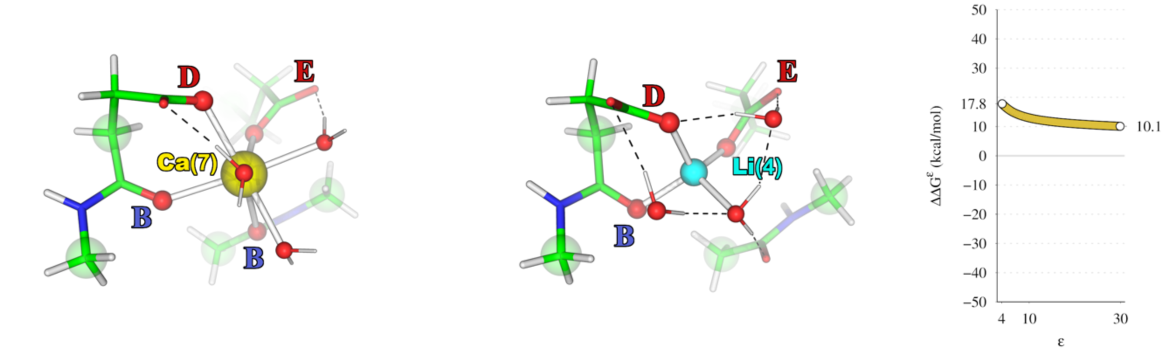
12


E
B
Ca(7)
Li(4)
ΔΔG^ε (kcal/mol)
18.5
16.5
ε

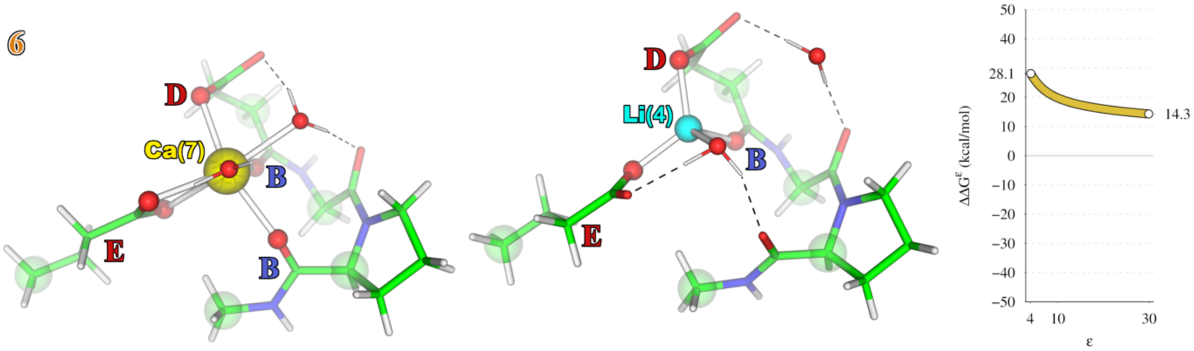
Supporting Information Figure S1l. Models for B_2D_2 Ca^{2+}-sites containing two backbone and two carboxylate ligands.



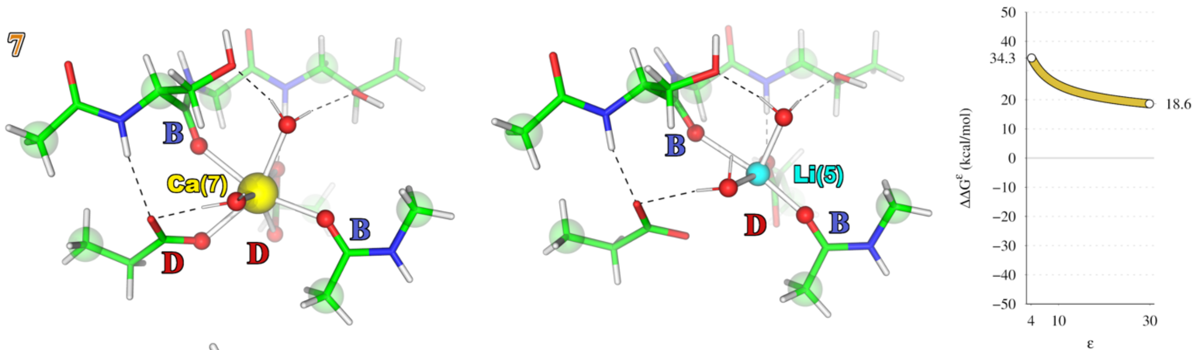
5


D
E
Ca(7)
B
B
D
E
Li(4)
B
ΔΔG^ε (kcal/mol)
17.8
10.1
ε
4
10
30

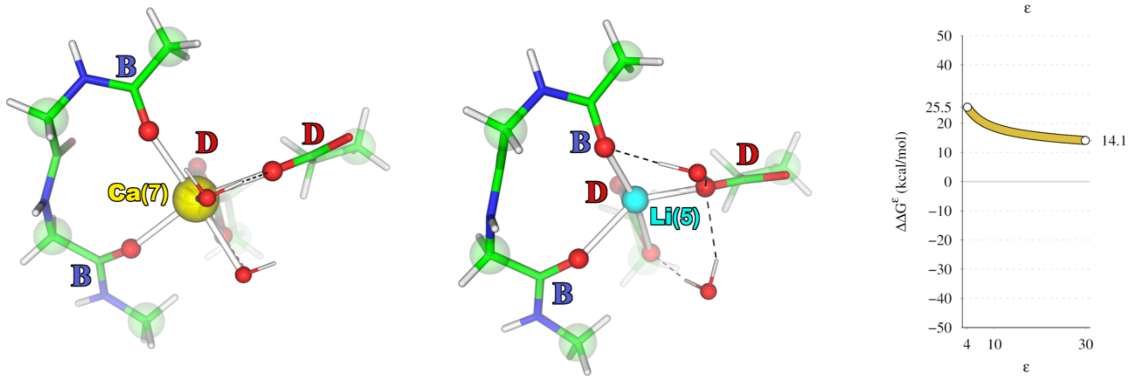
6


D
Ca(7)
B
E
B
D
Li(4)
B
E
ΔΔG^ε (kcal/mol)
28.1
14.3
ε
4
10
30

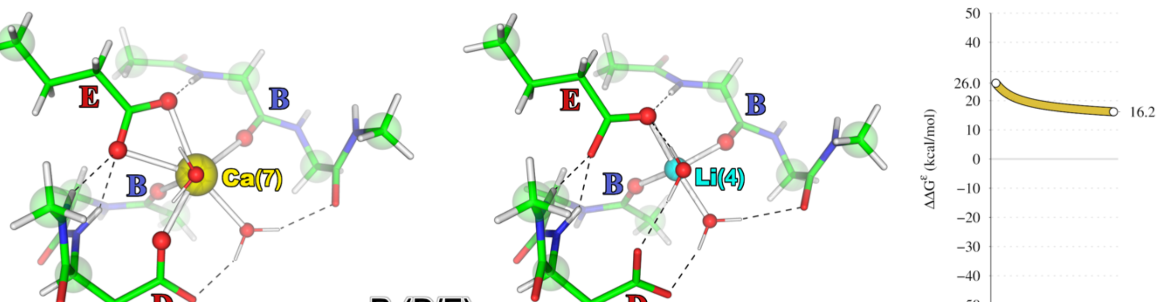
7


B
Ca(7)
D
D
B
B
Li(5)
D
B
ΔΔG^ε (kcal/mol)
34.3
18.6
ε
4
10
30

8

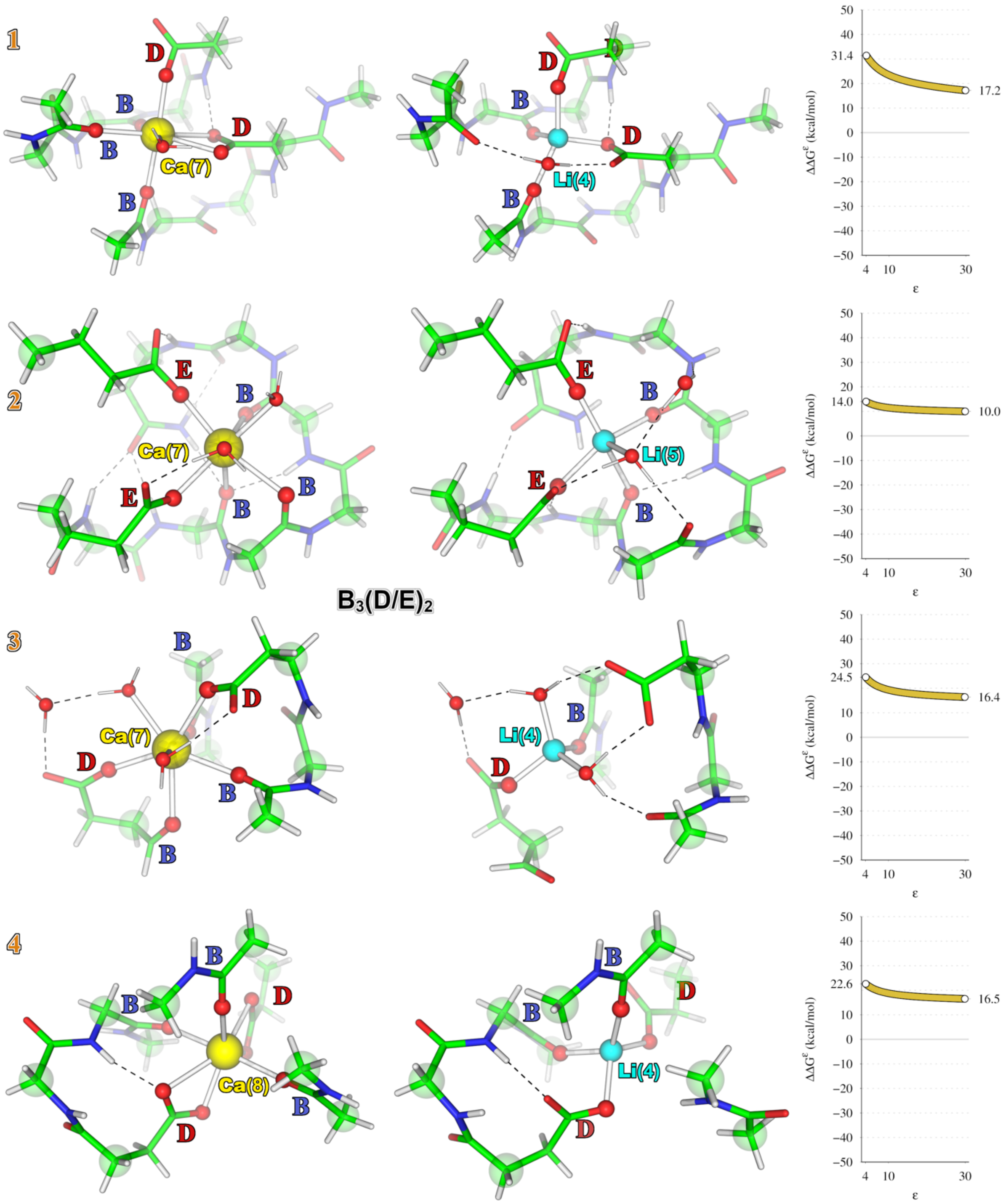

B
D
D
Ca(7)
B
B
D
D
Li(5)
B
ΔΔG^ε (kcal/mol)
25.5
14.1
ε
4
10
30

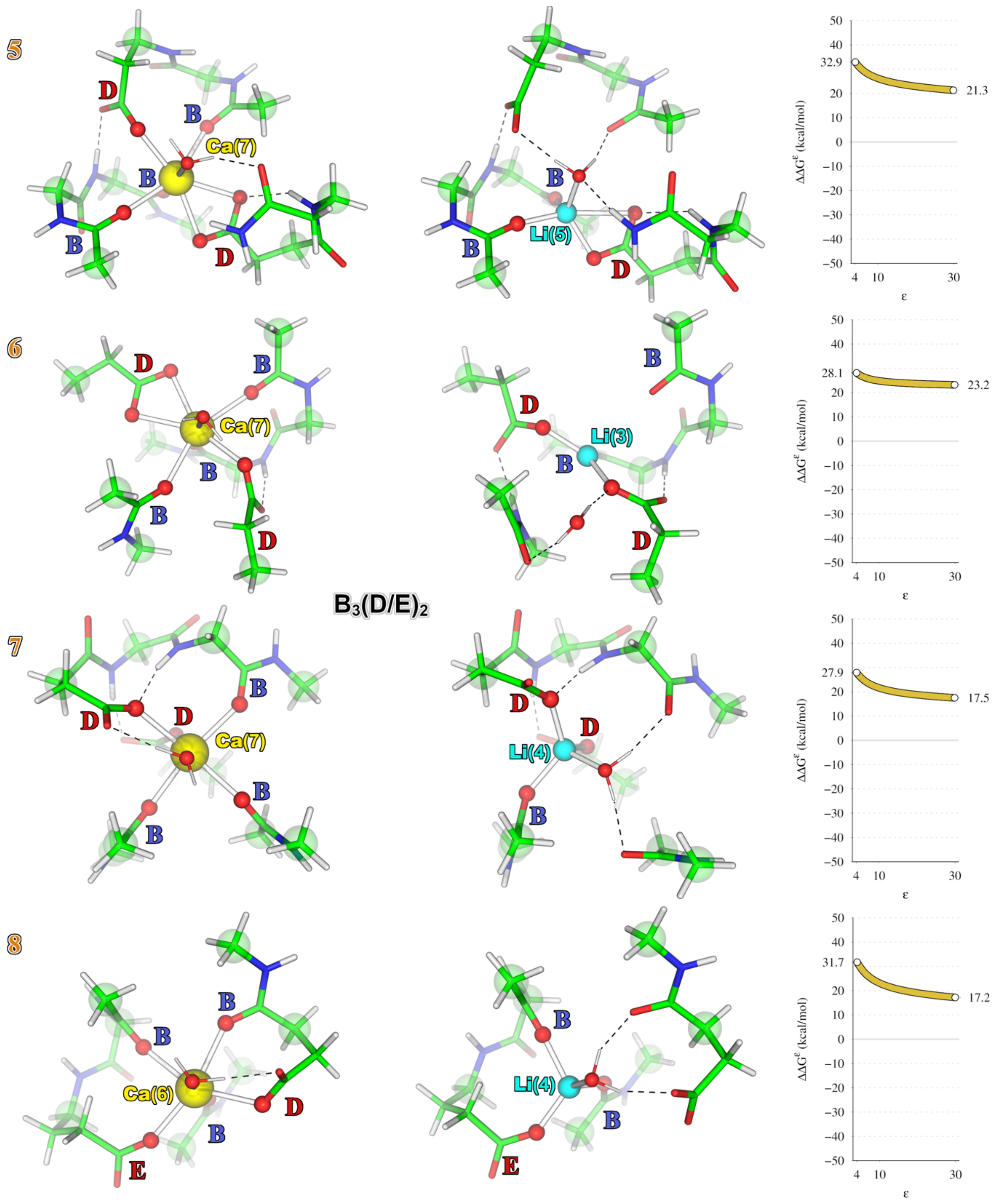
9


E
B
B
Ca(7)
D
E
B
B
Li(4)
D
ΔΔG^ε (kcal/mol)
26.0
16.2
ε
4
10
30

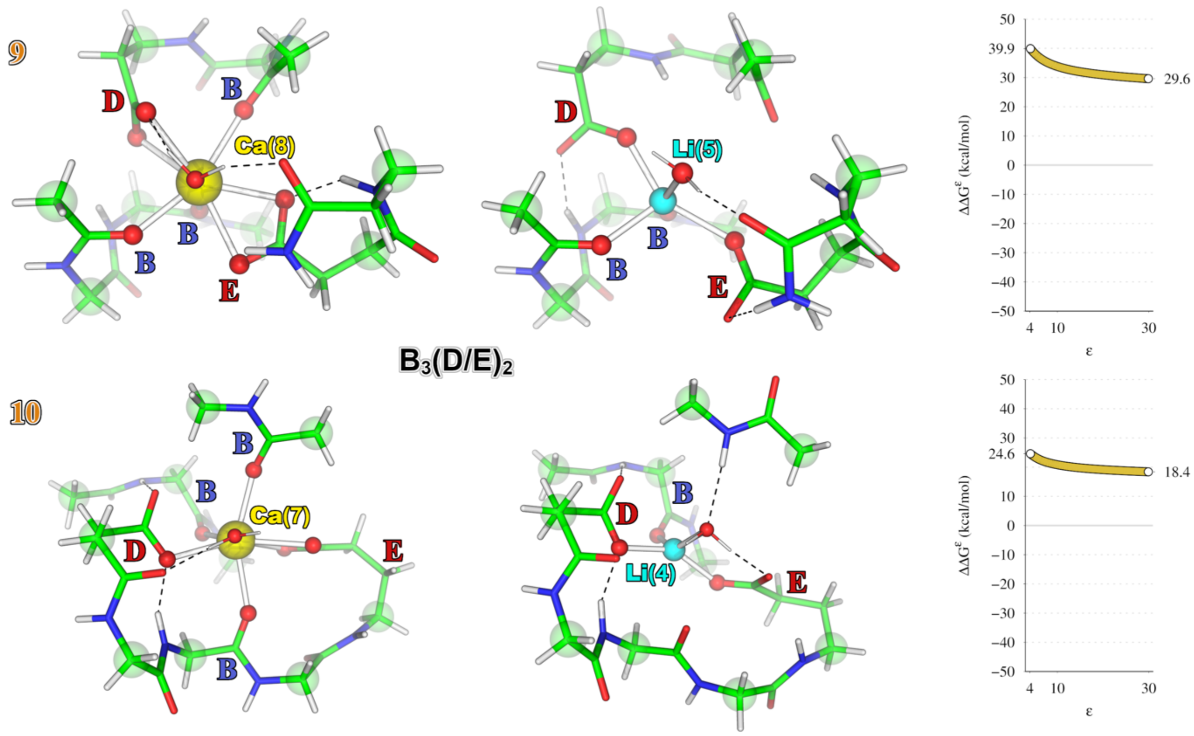
$B_2(D/E)_2$

Supporting Information Figure S1m. Models for B_3D_2 Ca^{2+}-sites containing three backbone and two carboxylate ligands.



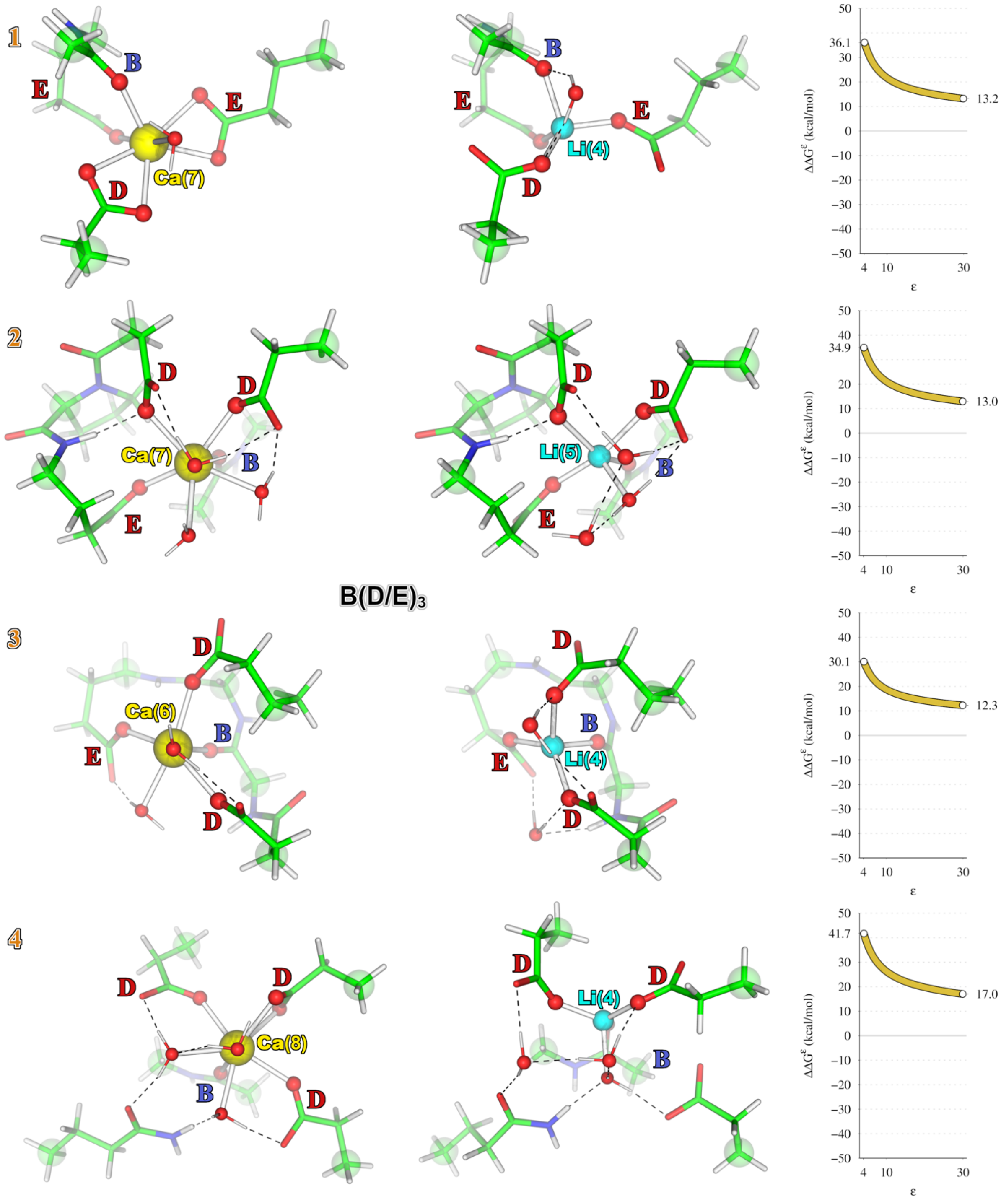


5
D
B
B
Ca(7)
B
D
Li(5)
32.9
21.3
ΔΔG^ε (kcal/mol)
ε
6
Ca(7)
Li(3)
28.1
23.2
B3(D/E)2
7
Ca(7)
Li(4)
27.9
17.5
8
Ca(6)
E
Li(4)
31.7
17.2

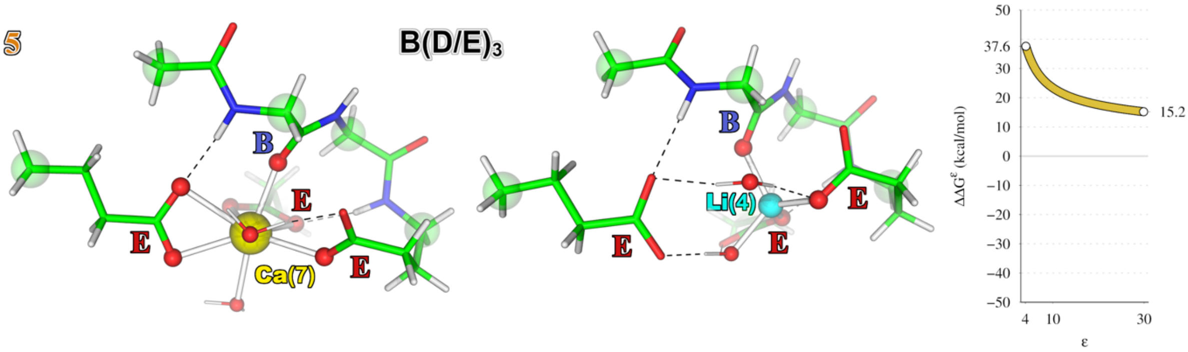


9
D
B
Ca(8)
B
B
E
D
Li(5)
B
B
E
B3(D/E)2
10
B
B
Ca(7)
D
E
B
D
B
Li(4)
E
50
39.9
30
29.6
20
10
0
−10
−20
−30
−40
−50
4
10
30
ε
ΔΔG^ε (kcal/mol)
50
40
30
24.6
18.4
10
0
−10
−20
−30
−40
−50
4
10
30
ε
ΔΔG^ε (kcal/mol)

Supporting Information Figure S1n. Models for B(D/E)$_3$ Ca^{2+}-sites containing a backbone ligand and three carboxylate ligands.

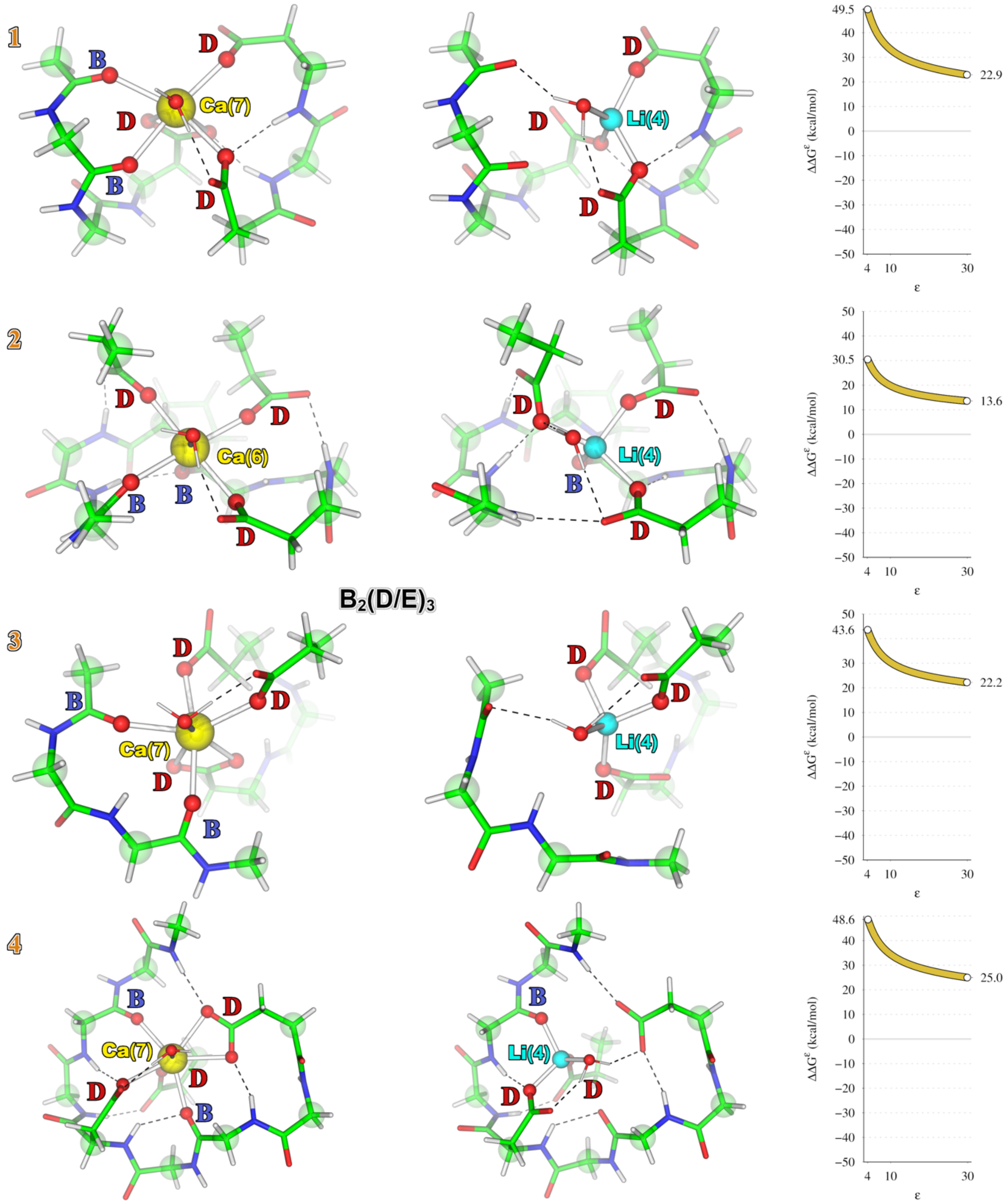


5

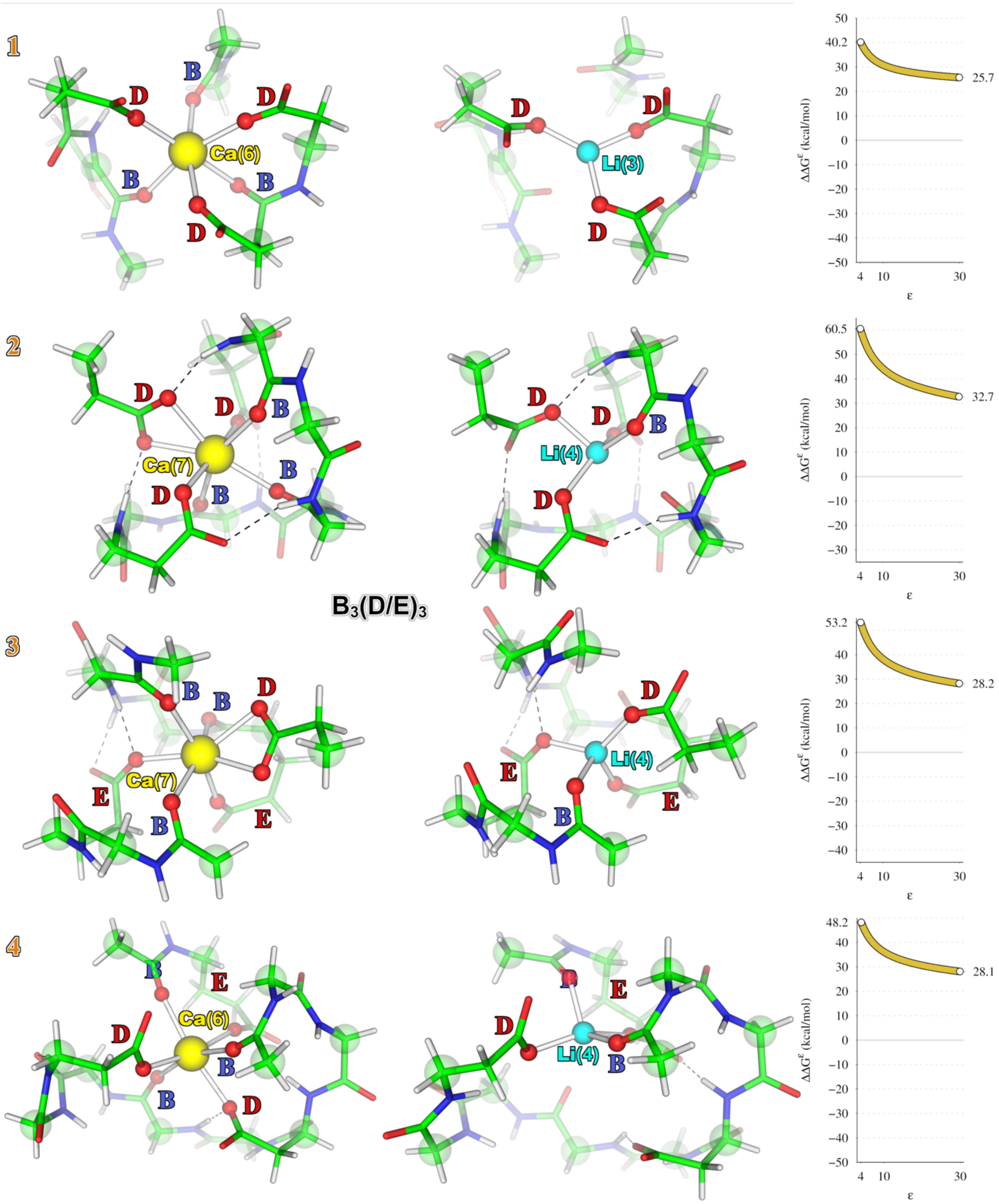


B(D/E)3
B
E
E
E
Ca(7)
B
E
Li(4)
E
E
50
37.6
30
20
10
0
−10
−20
−30
−40
−50
15.2
ΔΔG^ε (kcal/mol)
4
10
30
ε

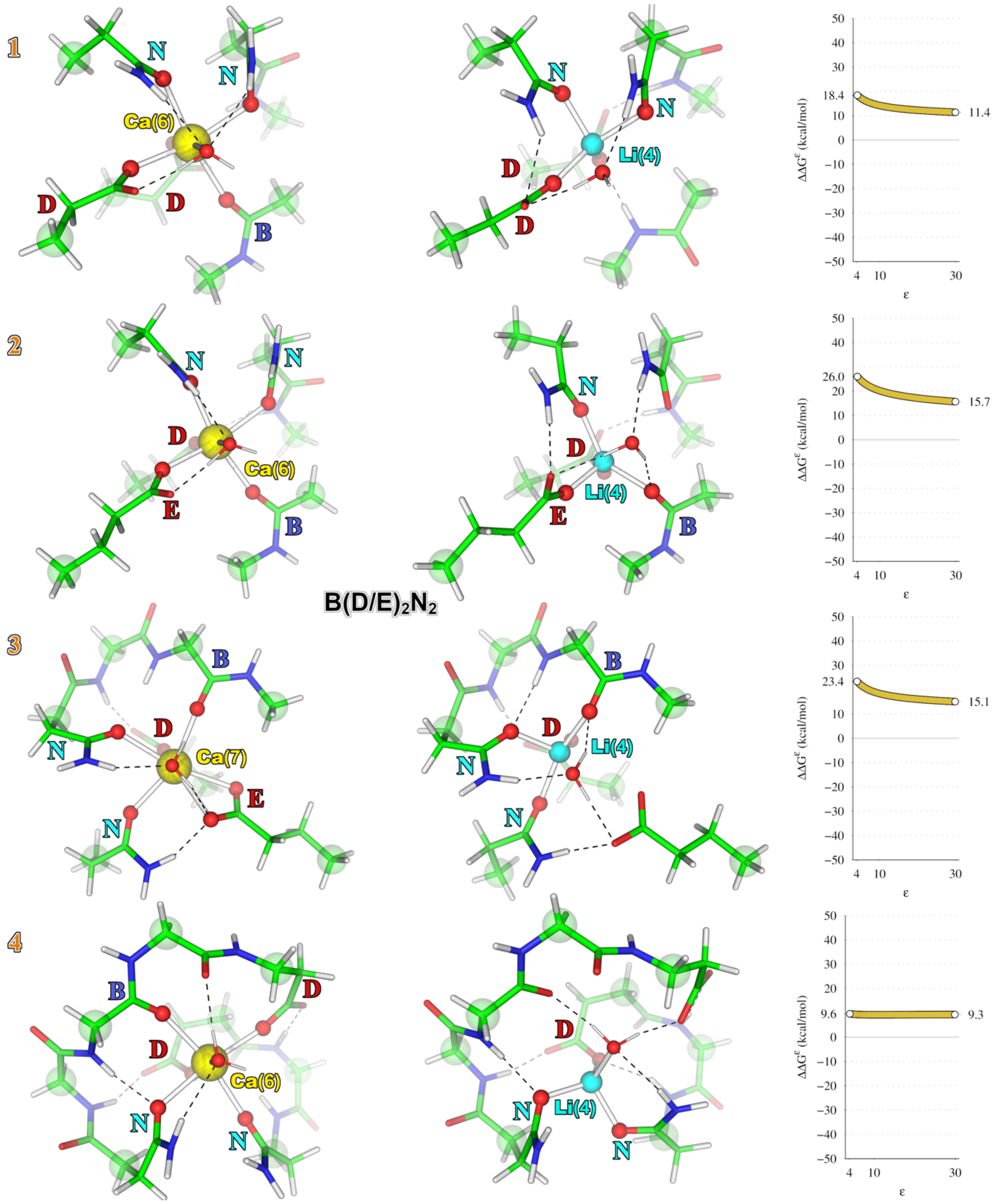
Supporting Information Figure S1o. Models for $B_2(D/E)_3$ Ca^{2+}-sites containing two backbone and three carboxylate ligands.

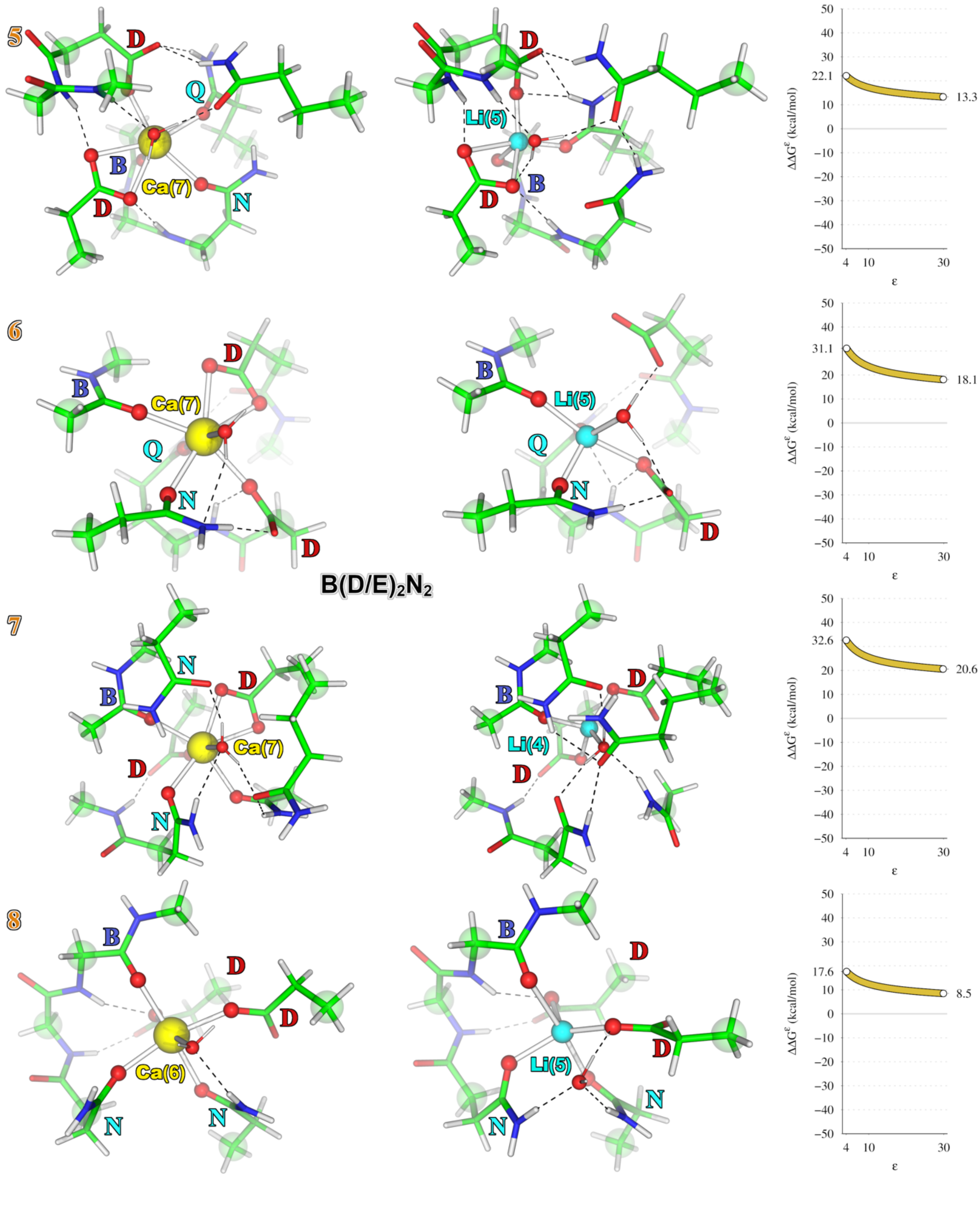


Supporting Information Figure S1p. Models for $B_3(D/E)_3$ Ca^{2+}-sites containing three backbone and three carboxylate ligands.



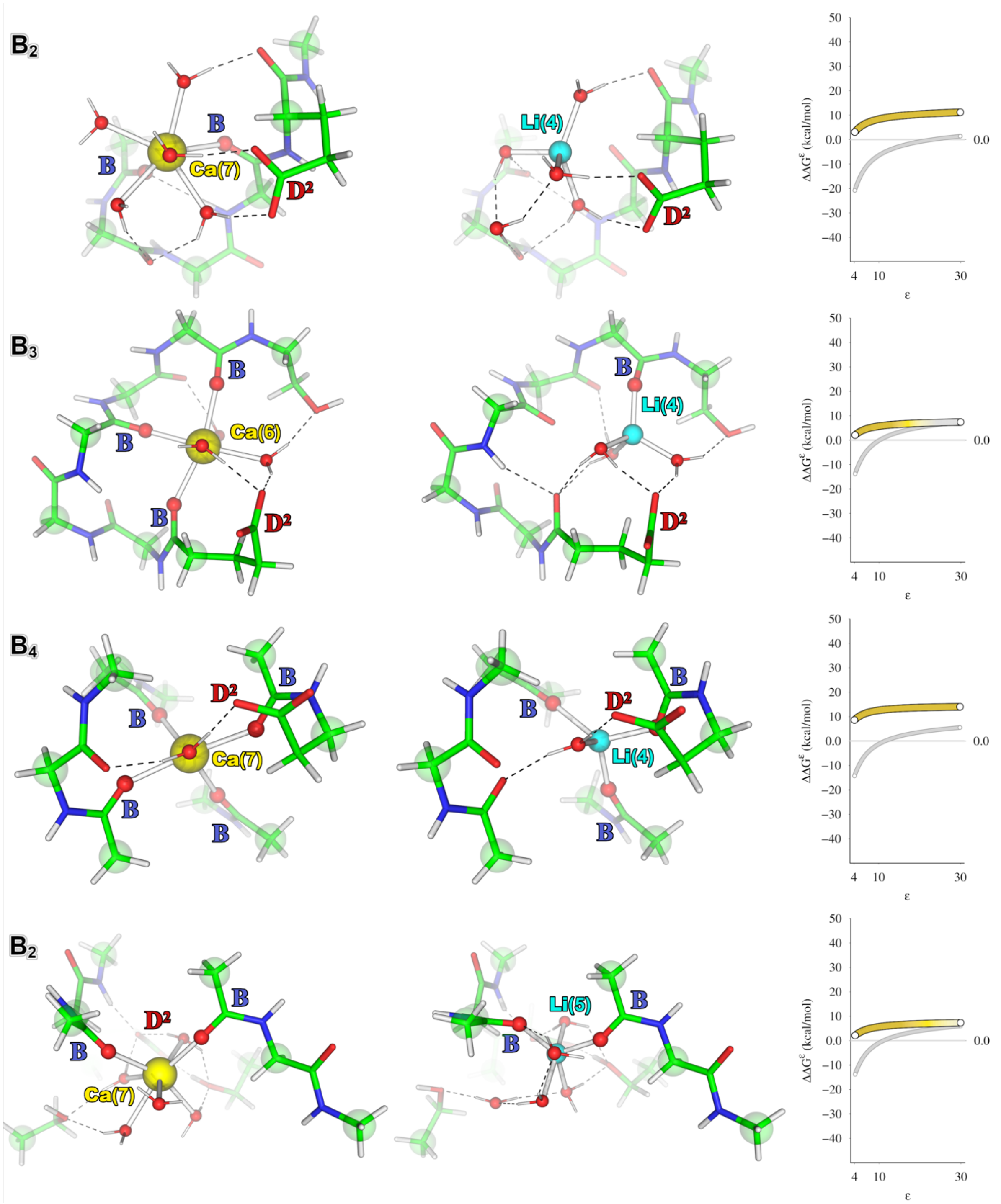
Supporting Information Figure S1q. Models for $BN_2(D/E)_2$ Ca^{2+}-sites containing three amide (1 backbone and two Asn/Gln) and three carboxylate ligands.



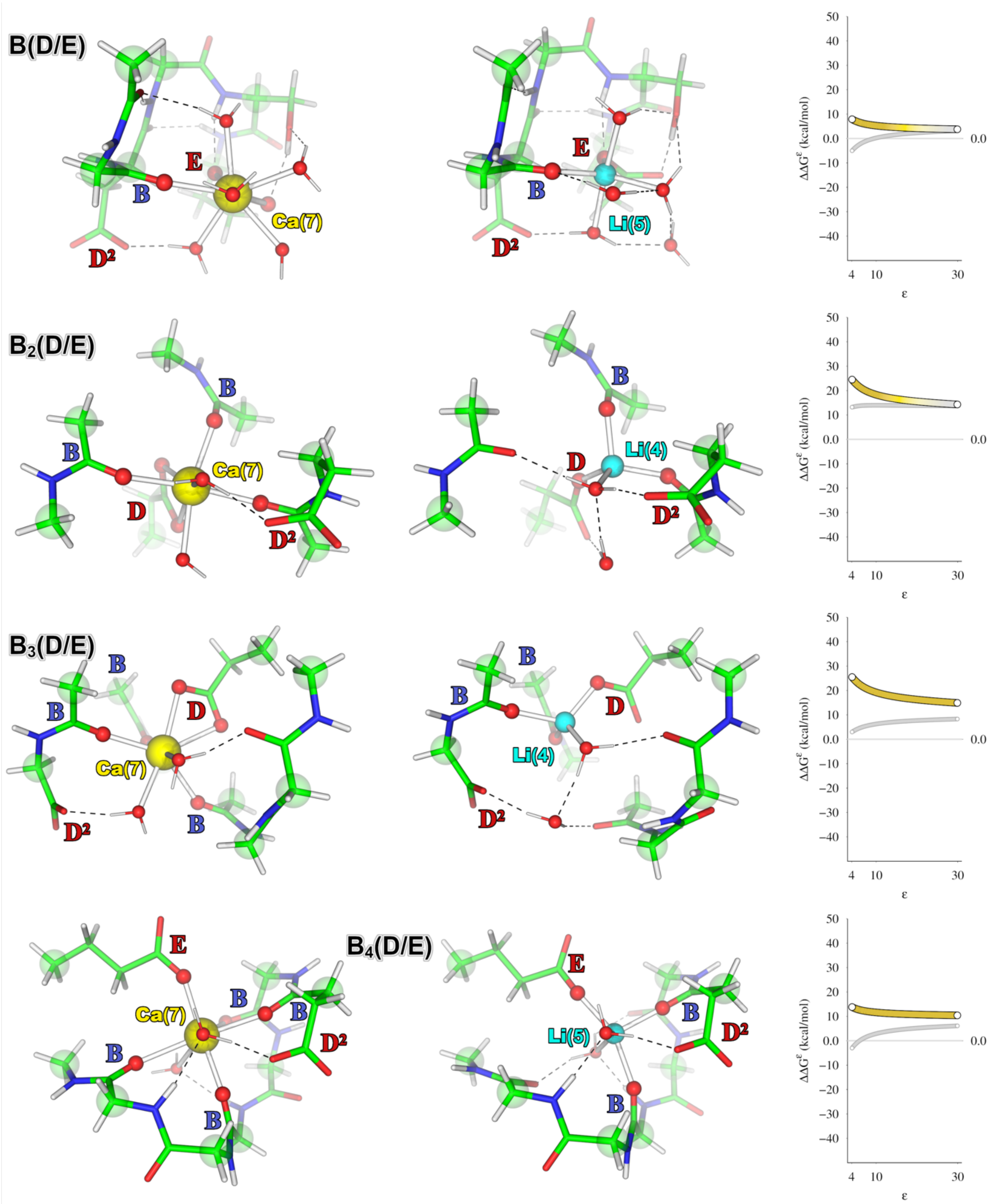


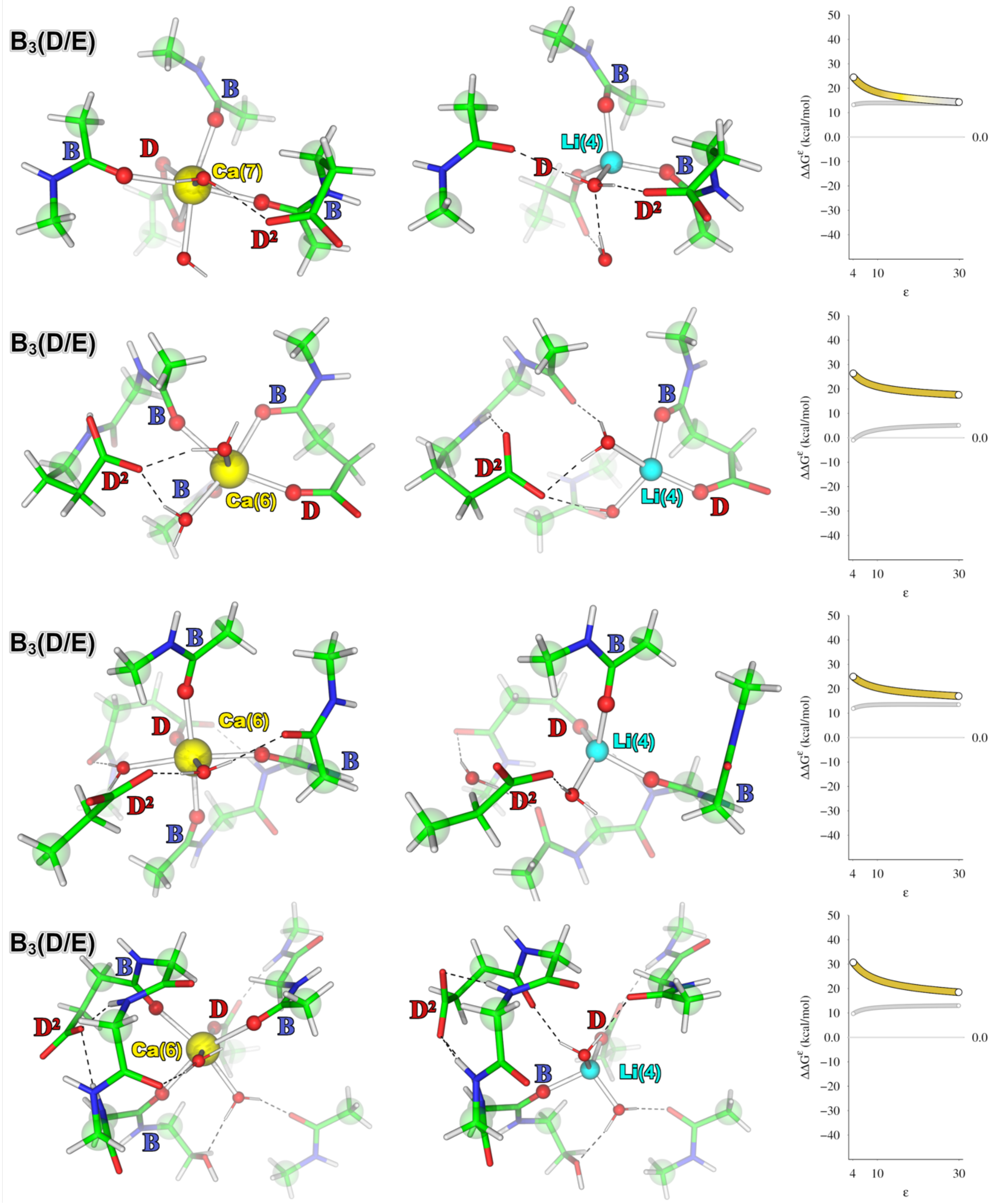
5
D
Q
B
Ca(7)
N
Li(5)
22.1
13.3
6
31.1
18.1
B(D/E)$_2$N$_2$
7
Li(4)
32.6
20.6
8
Ca(6)
17.6
8.5
$\Delta\Delta G^{\varepsilon}$ (kcal/mol)
ε
50
40
30
20
10
0
-10
-20
-30
-40
-50
4
10
30

Supporting Information Figure S1r. Models for B_x Ca^{2+}-sites with a 2nd-shell Asp/Glu. Relative metal exchange free energy of the B_xD Ca^{2+}-site without the 2nd-shell Asp/Glu is in grey for comparison. The thickest line corresponding to the system with 2nd-shell Asp/Glu is colored with a gradient reflecting the change of free energy compared with the site without 2nd-shell (yellow = more Ca-selective, blue = more Li-selective).



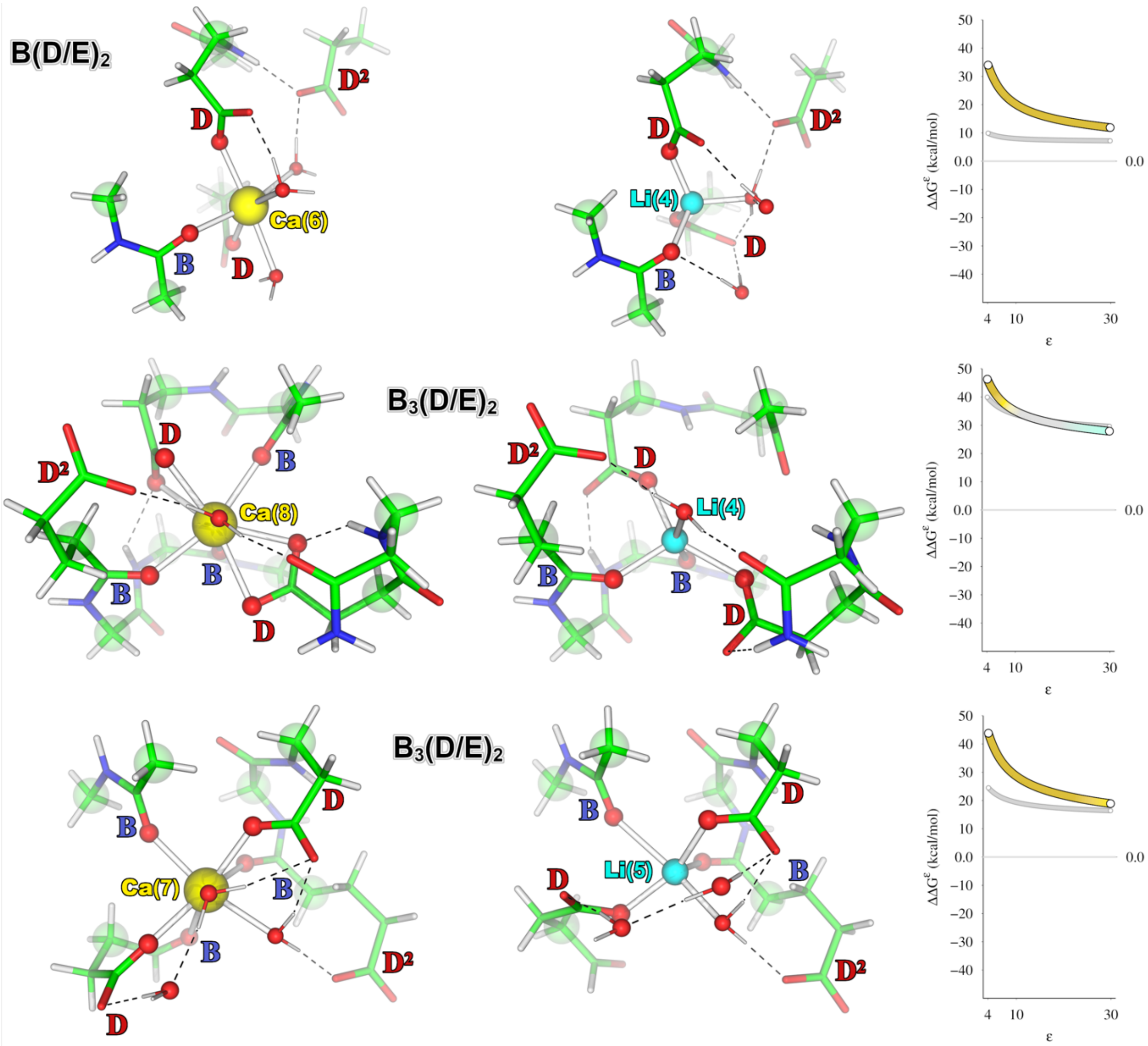
Supporting Information Figure S1s. Models for B_xD Ca^{2+}-sites with a 2nd-shell Asp/Glu. Relative metal exchange free energy of the B_xD Ca^{2+}-site without the 2nd-shell Asp/Glu is in grey for comparison. The thickest line corresponding to the system with 2nd-shell Asp/Glu is colored with a gradient reflecting the change of free energy compared with the site without 2nd-shell (yellow = more Ca-selective, blue = more Li-selective).



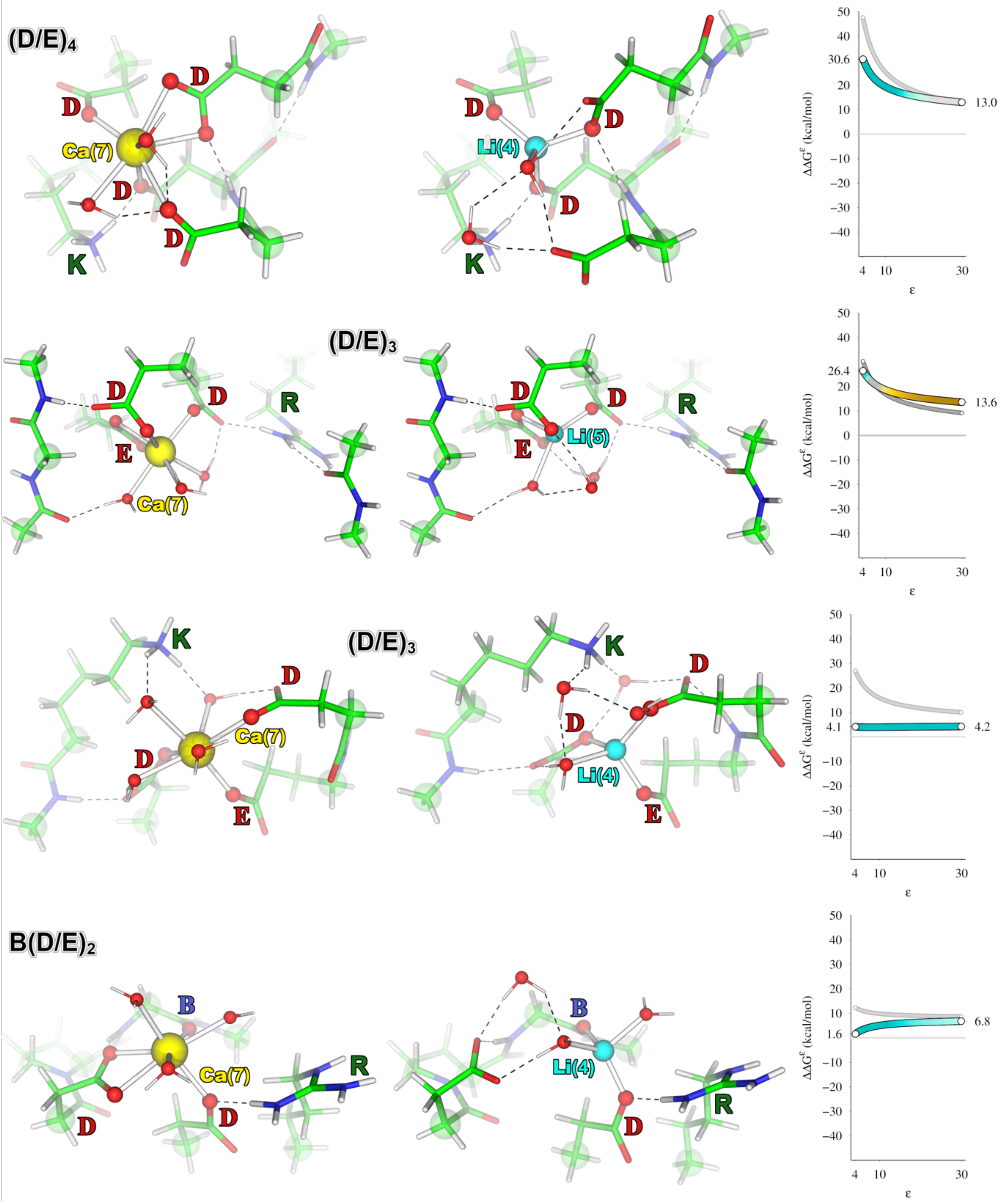


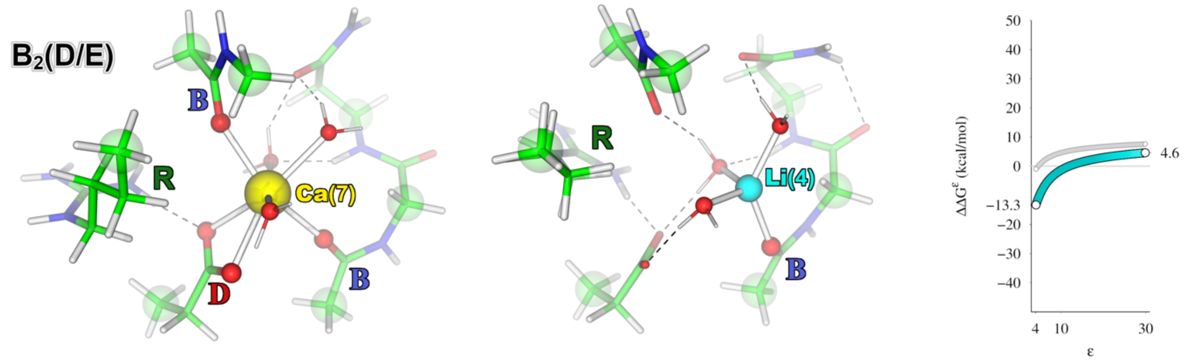
B_3(D/E)
B
D
Ca(7)
D^2
Li(4)
B_3(D/E)
Ca(6)
B_3(D/E)
Ca(6)
B_3(D/E)
Ca(6)
$\Delta\Delta G^{\varepsilon}$ (kcal/mol)
ε
0.0
50
40
30
20
10
0.0
−10
−20
−30
−40
4
10
30

Supporting Information Figure S1t. Models for B_xD_2 Ca^{2+}-sites with a 2nd-shell Asp/Glu. Relative metal exchange free energy of the B_xD Ca^{2+}-site without the 2nd-shell Asp/Glu is in grey for comparison. The thickest line corresponding to the system with 2nd-shell Asp/Glu is colored with a gradient reflecting the change of free energy compared with the site without 2nd-shell (yellow = more Ca-selective, blue = more Li-selective).



Supporting Information Figure S1u. Models for B_xD_x Ca^{2+}-sites with a 2nd-shell Arg/Lys. Relative metal exchange free energy of the B_xD_x Ca^{2+}-site without the 2nd-shell Arg/Lys is in grey for comparison. The thickest line corresponding to the system with 2nd-shell Arg/Lys is colored with a gradient reflecting the change of free energy compared with the site without 2nd-shell (yellow = more Ca-selective, blue = more Li-selective).





B2(D/E)
B
R
Ca(7)
D
B
R
Li(4)
B
50
40
30
20
10
0
−13.3
−20
−30
−40
4.6
ΔΔG^ε (kcal/mol)
4
10
30
ε