

BCH 258 lecture notes Mon. Sept 12, 2011: Roles of Amino Acids, mutations

Roles of the Amino Acids, and mutations to replace them

review_Wrksht3_handedAAroles2009) for illustrations of sidechain roles. Emphasis in Wrksht3 and in background section below is on static relationships of amino acid properties and structure. Major emphasis today is synergistic roles in change and dynamic processes.

- Handouts: aaLayout.pdf
- Assignment: WrkSht7-mutations2009: DUE MONDAY SEPT 19
- Kinemages: 1lmb6_85aH.kin, 1lmb6_85aH.pdb, 2simHdot.kin, 2simH.pdb,

TSPases.kin : TrypsinSubtilisinPapain: site aa similar roles in different structures.

2PTC, 1CSE, 3EIZ : “Catalytic Triad” always a Tetrad to spread charge.

serine (and cysteine) proteases attack mc C and stabilize mc O in OXYanion hole.

RXN: Ser—O → C=O, C goes through tetrahedral intermediate with O⁻ stabilized, becomes acylated enzyme, broken part leaves,

Water—O → C=O of acylated E → Tetrahedral Intermediate → released Product Peptide.

Nature of Amino Acids and geometry of Protein Structure work together to perform reaction.

Graphics: All-atom contacts : (recall howdotwork3KiNG.kin)

- Mutation check: 1lmb6_85aH.kin : in class: show Thr 8 → Val does NOT work!
(WorkSheet homework: show Tyr 22 → Trp does work!)
Thr 8 → Asn NOT work, Asn 58 → Gln NOT work, (Gly 43 → Ser NOT work)
Good N-cap residues, 2 sets: Ser, Thr vs. Asn, Asp

BACKGROUND

Hydrophobic “H” vs Polar “P” : is the most important parameter

“HP” pattern in sequence determines approx. 3D fold, putting most H in, P out

- 1snm.1.kin, 1snm.somap.gz H in, P out - views of Helix and Loop regions.
Drop 1SNM.pdb on KiNG: open in Molikin: just do balls on sidechain O,N,S,...
- 1us0FH-multi_BCH258.kin works well for this also., use 1us0.scBalls.kin
“H” : function of Hydrophobic surface area (but Cys also strongly buried)
“P” : function of charge, H-bonding, polarizability (but Pro out, forming corners)
alternating “HP” favors $\uparrow\downarrow\beta$; 3.5 period favors α helix; a run of “P” favors turns;
long run of “H” favors transmembrane; short run of “H” favors $\uparrow\uparrow\beta$

Size, shape, & flexibility of sidechain

Mainchain flexibility: Gly > Ala (and others) > branched C β > Pro > SS

Entropy mutants (native vs unfolded): SS, A → P, G → A

Sidechain degrees of freedom: Hydrophobics ≤ 2 chi's (χ) (except Met 3))

many Polars have more, esp/ Lys & Gln very loose

Aromatics (FYWH): big & flat, help constrain packing

slightly + on edge, - on face,

more often perpendicular than stacked

Pro: not aromatic, not flat; puckers up or down at C γ

ring constrains ϕ near -60° ; good at turns;

good in N-term end of α helix

can do α middle, but bends helix

Ile, Thr sidechains handed: long arm, or Og, on “left” side (arms in front of body)

Sidechains “rotameric”, i.e. few preferred conformations; Ctetr near staggered

Sidechain angles: χ_1, χ_2 , etc. dihedrals (χ_4 max, for Lys & Arg)

for bonds between tetrahedral carbons, staggered >> eclipsed

overall, a few well-defined sidechain conformations are good: rotamers

[only 2 good (4 more OK) for Leu; 13 for Met with 3 χ angles and no branches].



Secondary-structure preferences

Loop, turn, coil : Gly, Ser, Asn, Pro, & charges best; Hydrophobics poor

Beta : branched C β 's best (Val, Ile, Thr); Pro, Asn worst

Helix : in middle: Ala, Leu, Met, Gln best; Pro worst

near beginning – charge good (Asp, Glu); near end + charge good (Lys, Arg, His)

N-cap : Asp, Asn, Ser, Thr best (sc H-bond to mc NH of N-cap +3 or +2)

N-cap +1 : Pro best

C-cap : Gly best (usually has + ϕ value)

pair of touching Hydrophobics often bracket N or C caps

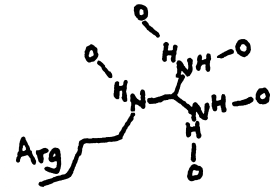
Pair comparisons (What is a conservative replacement?)

Arg ordered, H-bonded (5-planar O's),

vs **Lys** often disordered, helps solubility

E.G.: 1us0FH-multi_BCH258.kin, 1us0.omap.gz:

water ON, search cd arg and cd lys ...



Leu one of best for helix,

vs **Ile** one of best for β -sheet

Asn backbone mimic, best non-Gly for + ϕ conf.; strong pref.s;
amide constrained

vs **Gln** “plain vanilla” residue: good α , OK most places;

amide very free

Asn one of best N-caps, Gln is worst (note extra atom E vs N)

Gln one of best at specific DNA base H-bonds,

Asn too short & wrong angles



Multiple roles: distinguish by substitution pattern in aligned sequences

Arg: +charge (sub=Lys); oriented H-bonds (sub=Gln); Hydrophobic (sub=Tyr, Leu, Ile)

Gly: flexibility (sub=Ser); small size (sub=Ala or none); + ϕ conf. (sub=Asn)

His: titrates near pH 7 (no sub); +charge (sub=Lys, Arg); H-bonds (sub=Gln, Asn);

metal ligand (sub= Cys, Asp, Glu)

Cys: buried SH (sub=Hydrophobics); SS (sub=Hydrophobics, rarely);

metal ligand (sub=His, Asp, Glu, rarely)