**SUPPORTING INFORMATION**

(Tables S1-S4)

# Conformational landscape of substituted prolines

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**Table S1**. Dihedral angles of α-substituted proline analogues in CSD.

| trans /cis | name | $\phi$° | $\psi$° | $\chi_2$ [a] ° | d [b] | $\theta$ [c] ° | CSD code |
|---|---|---|---|---|---|---|---|
| ***trans*** | | | | | | | |
| | Ac-(2Me-Pro)-NHMe | –60 | –25 | 36 | 3.00 | 121.8 | BIJDUT10 |
| | Ac-(2Me-Pro)-OMe | –45 | –40 | 41 | 2.71 | 110.5 | QECWON |
| | Cbz-(2Me-Pro)-OH | 56 | 33 | –38 | 2.92 | 115.7 | NUKSES |
| | 4-BrBz-(2Ph-Pro)-$NH_2$ | 76 | –55 | 43 | 3.27 | 173.5 | LIVSUF |
| | 2-ClBz-(2Ph-Pro)-$NH_2$ | 78 | –37 | 41 | 3.30 | 169.6 | MOPKAD |
| | 2-Fur-(2Ph-Pro)-$NH_2$ | 78 | –55 | 43 | 3.27 | 175.4 | MOPKEH |
| | 4-Br-PhAc-(2(4$NO_2$-Ph) Pro)-O$^t$Bu | –49 | –48 | 35/ –27 | 2.72 | 102.4 | GABWOX |
| | (Phe)$_2$N-CO-(2$N_3$-Pro)-OMe | –60 | 153 | –35 | 2.83 | 94.4 | ZIKNAI |
| | 2-BrBz-(2(4Cl-Ph)-Pro)-$NH_2$ | 81 | –46 | 41 | 3.34 | 175.9 | ZICBUK |
| | Tfa-(2(1-(3-Hydroxylphenyl) | 59 | n.d. | 40 | 3.35 | 172.3 | LIPGIC |
| | prop-2-en1-yl)-Pro-OMe | 82 | n.d. | 40 | 2.94 | 160.4 | LIPGIC |
| ***cis*** | | | | | | | |
| | Boc-(2Me-Pro)-OH | –52 | –33 | 39 | 4.13 | 145.8 | XETSOG |
| | Boc-(2Ph-Pro)-OH | 42 | 46 | –36 | 4.16 | 136.3 | EVOPOU |
| | Boc-(2Vin-Pro)-OH | –47 | –38 | 40 | 4.20 | 143.3 | UHOLOA |
| | Boc-(2(2F-Bn)-Pro)-OH | –55 | 157 | 36/ –34 | 4.11 | 71.8 | AFIXOE |

[a] The *exo* and *endo* ring puckers are shown in blue and red, respectively.

[b] 'd' corresponds to the distance (in Å) between carbonyl oxygen atom ($O_{i-1}$) of the residue preceding Pro (or analog) and the carbon atom of the carbonyl group of Pro (or analog) $>C_i=O_i$.

[c] $\theta$ corresponds to the angle between $O_{i-1}$, $C_i$ and $O_i$.

**Table S2**. Dihedral angles of 4-substituted proline analogues [a] in CSD.

| compound | $\phi$ ° | $\psi$ ° | $\chi_2$ [b] ° | d [c] | $\theta$ [d] ° | CSD code |
|---|---|---|---|---|---|---|
| ***trans*-(2*S*,4*R*)** | | | | | | |
| Ac-Mep-$NHCH_3$ | –78 | –21 | –36 | 3.18 | 120.1 | CADRAE |
| Boc-(4(4I-PhO-Pro)-$OCH_3$ | –52 | –39 | 38 | 2.84 | 109.7 | GABPEH |
| Boc-Hyp-$OCH_3$ | –55 | –32 | 41 | 2.89 | 116.3 | INEMIX |
| Ac-Hyp-OH | –60 | –31 | 39 | 2.85 | 115.5 | POKKAD |
| Ac-Hyp-$OCH_3$ | –63 | 156 | 36 | 2.90 | 92.4 | RISDAY |
| Ac-Hyp-$OCH_3$ | –51 | 145 | 40 | 2.75 | 91.3 | RISDAY |
| Ac-Flp-$OCH_3$ | –55 | 140 | 38 | 2.75 | 99.1 | RISDEC |
| Ac-Flp-$OCH_3$ | –56 | 141 | 38 | 2.78 | 97.4 | RISDEC |
| Ac-Mop-$OCH_3$ | –58 | 148 | 37 | 2.84 | 94.6 | SODJEB |
| Ac-Clp-$NHCH_3$ | –77 | –18 | –37 | 3.16 | 121.6 | VEFBOZ |
| Ac-Azp-$OCH_3$ | –60 | 147 | 36 | 2.85 | 97.7 | WETNAL |
| Boc-(*p*Tos-O)-Pro-OBn | –59 | 148 | 37 | 2.89 | 93.5 | YEJHEC |
| ***trans*-(2*S*,4*S*)** | | | | | | |
| Ac-mep-$NHCH_3$ | –74 | –14 | 34 | 3.14 | 126.8 | CADREI |
| Ac-mep-$NHCH_3$ | –71 | –18 | 35 | 3.09 | 124.6 | CADREI |
| BrBz-(Boc)-Pro-O$^t$Bu | –75 | –14 | 37 | 3.20 | 125.5 | HALTAR |
| Tfa-(4OBn-Pro)-NHCy | –69 | 176 | –38 | 3.12 | 77.0 | KULQIT |
| Tfa-(4OBn-Pro)-NHCy | –74 | 179 | –39 | 3.15 | 79.6 | KULQIT |
| Ac-(4$NH_3^+$-Pro)-$OCH_3$ | –74 | 157 | –34 | 3.01 | 95.1 | NAFKAJ |
| Boc-(4$^t$Bu)-Pro-O$^t$Bu | –76 | 157 | –37 | 3.12 | 95.5 | RARMUT |
| Bz-(4$MeSO_2O$-Pro)-OH | –85 | –178 | –36 | 3.28 | 84.7 | TUHMEO |
| Ac-clp-$NHCH_3$ | –59 | 149 | 35 | 2.92 | 93.5 | VEFBIT |
| Ac-clp-$NHCH_3$ | –52 | 147 | 36 | 2.86 | 100.3 | VEFBIT |
| ***trans*-(2*R*,4*R*)** | | | | | | |
| Ac-($CF_3$-Pro)-$OCH_3$ | 61 | 37 | –36 | 2.89 | 111.2 | YUCBUV |
| ***trans*-(2*R*,4*S*)** | | | | | | |
| Tfa-hyp-$NHC_6H_3F_2$ | 63 | –139 | –39 | 2.95 | 103.1 | GAZGOG |
| Ac-hyp-OH | 61 | 30 | –40 | 2.86 | 115.5 | NAHYPL |
| ***cis*-(2*S*,4*R*)** | | | | | | |
| Boc-(4Vin-Pro)-OH | –58 | –30 | 37 | 4.19 | 145.9 | PIGYEL |
| Boc-(4$MeSO_2O$-Pro)-O$^t$Bu | –55 | –22 | 39 | 4.37 | 152.8 | PEQVIT |
| Ac-Azp-$OCH_3$ | –82 | 173 | –35 | 4.39 | 77.9 | WETNAL |
| Boc-(4Ph-Pro)-OH | –73 | 148 | 40 | 4.37 | 91.6 | QUDVUG |
| ***cis*-(2*R*,4*R*)** | | | | | | |
| Boc-$^D$Mop-OH | 86 | –16 | 41 | 4.42 | 171.19 | WADVOO |
| ***cis*-(2*S*,4*S*)** | | | | | | |
| Boc-($4CF_3$-Pro)-OH | –66 | 177 | 40 | 4.28 | 73.7 | MOGQOO |
| Boc-(4$^t$Bu-Pro)-OH | –75 | –10 | –34 | 4.33 | 67.0 | RARNAA |
| Boc-mop-OH | –85 | 18 | –41 | 4.40 | 171.8 | EMITIE |
| Boc-cnp-OH | –78 | n.d. | –32 | 4.31 | n.d. | TALBUD |
| Ac-hyp-Ome | –84 | 18 | –38 | 4.41 | 172.7 | EMITEA |
| Boc-(4(4I-pho-Pro)-OH | –76 | 1 | –38 | 4.38 | 163.1 | GABNUV |
| Fmoc-(4(4I-pho)-Pro)-OH | –83 | 177 | –37 | 4.41 | 78.9 | GABPAD |
| Boc-Hyp-OPhAc | –65 | 145 | 38 | 4.26 | 89.6 | FICZEX |

[a] Stereochemistry of the 2- and the 4- positions are grouped.

[b] The exo and the endo ring pucker are indicated in blue and red, respectively.

[c] 'd' corresponds to the distance (in Å) between carbonyl oxygen atom ($O_{i-1}$) of the residue preceding Pro (or analog) and the carbon atom of the carbonyl group of Pro (or analog) $>C_i=O_i$.

[d] $\theta$ corresponds to the angle between $O_{i-1}$, $C_i$ and $O_i$.

**Table S3**. Dihedral angles of 3-substituted proline analogues in CSD.

| compound | abs. config | hydrogen replaced | $\phi$ ° | $\psi$ ° | $\chi_2$ [a] ° | d [b] | $\theta$ [c] ° | CSD |
|---|---|---|---|---|---|---|---|---|
| **L-proline/*trans*** | | | | | | | | |
| Ac-(3F-Pro)-OMe | 2R,3R | 3R | -56 | 151 | 37 | 2.81 | 90.8 | LEWPAF |
| Ac-(3Me-Pro)-NHMe | 2S,3R | 3R | -79 | 146 | -40 | 3.23 | 105.1 | BIJFAB10 |
| Ac-(3F-Pro)-OMe | 2R,3S | 3S | -71 | 158 | -35 | 3.08 | 95.4 | LEWXER |
| Boc-(3Ph-Pro)-$^{D}$Phe-NHMe | 2S,3R | 3S | -56 | 127 | 39 | 2.79 | 106.4 | BAPNEV |
| Ac-(3(4-Cl-Ph)-Pro)-NHR | 2S,3R | 3S | -51 | 138 | 41 | 2.72 | 97.0 | IFAXET |
| Ac-(3(4-Cl-Ph)-Pro)-NHR | 2S,3R | 3S | -59 | 140 | 42 | 2.86 | 99.5 | IFAXET |
| Boc-(3Ph-Pro)-$^{D}$Phe-NHMe | 2S,3R | 3S | -55 | 131 | 35 | 2.81 | 103.2 | BAPVEV |
| Ac-(3OH-Pro)-NHMe | 2S,3S | 3S | -79 | 164 | -39 | 3.20 | 94.7 | EHUNEA |
| Ac-(3Me-Pro)-NHMe | 2S,3S | 3S | -64 | -36 | 41 | 2.94 | 109.7 | CEDPUW |
| Boc-(3$CF_3$-Pro)-NHCH($CH_3$Ph) | 2S,3S | 3S | -85 | 145 | -35 | 3.29 | 109.5 | SIGJUQ |
| Boc-(3$CF_3$-Pro)-NHCH($CH_3$Ph) | 2S,3S | 3S | -73 | 135 | -32 | 3.10 | 111.0 | SIGJUQ |
| Boc-(3$CF_3$-Pro)-NHCH($CH_3$Ph) | 2S,3S | 3S | -58 | 126 | 34 | 2.89 | 110.5 | SIGJUQ |
| **D-proline/*trans*** | | | | | | | | |
| Cbz-(3iPr-Pro)-OH | 2R,3S | 3R | 50 | 46 | -34 | 2.79 | 101.4 | AWAVUQ |
| Moc-(3(1-Cl-Pr)-$^{D}$Pro)-OMe | 2R,3S | 3R | 61 | -157 | -39 | 2.93 | 88.8 | WEJSOT |
| Ac-(3(4-Cl-Phe)-Pro)-NHR | 2R,3R | 3S | 79 | -156 | 38 | 3.12 | 99.4 | WOBLAB |
| **L-proline/*cis*** | | | | | | | | |
| Boc-(3Ph-Pro)-OBn | 2S,3R | 3S | -56 | 137 | 41 | 4.17 | 82.8 | DOSFIB |
| Boc-(3OH-Pro)-OtBu | 2S,3S | 3S | -66 | 157 | -35 | 4.20 | 76.6 | DIDXUM |
| Boc-(3carboxy)-Pro)-OBn | 2R,3S | 3S | 79 | -151 | 39 | 4.31 | 85.6 | TAZPOZ |
| Boc-(3Ph-Pro)-OMe | 2S,3S | 3R | -59 | 149 | -38 | 4.18 | 82.4 | BALMOR |
| Boc-(3caboxy-Pro)-OH | 2S,3S | 3S | -58 | -33 | -32 | 4.22 | 141.8 | SUMZOP |
| Boc-(3*n*Pr-Pro)NH(CHC$H_3$Ph) | 2S,3S | 3S | -53 | 138 | 33 | 4.24 | 88.2 | KEBVAO |
| Boc-(3$CF_3$-Pro)-NHCH($CH_3$Ph) | 2S,3S | 3S | -63 | 141 | 38 | 4.27 | 84.5 | SIGJUQ |
| **D-proline/*cis*** | | | | | | | | |
| Boc-(3$CF_3$-$^{D}$Pro)-NHCH($CH_3$Ph) | 2R,3S | 3S | 92 | -151 | 41 | 4.47 | 89.7 | SIGKAX |
| Boc-(3Vin-$^{D}$Pro)-OH | 2R,3S | 3S | 76 | -171 | 38 | 4.32 | 76.6 | AWAVOK01 |
| Boc-(3Ph-Pro)-Obn | 2R,3R | 3S | 65 | -138 | 38 | 4.20 | 82.4 | DOSFIB |
| Boc-(3Ph-Pro)-Obn | 2R,3S | 3R | 55 | -138 | -40 | 4.18 | 81.8 | DOTVOY |
| Boc((3Ph-$^{D}$Pro)-OMe | 2R,3S | 3R | 57 | -147 | 37 | 4.16 | 82.3 | MISLEH |

[a] The *exo* and *endo* ring puckers are shown in blue and red, respectively.

[b] 'd' corresponds to the distance (in Å) between carbonyl oxygen atom ($O_{i-1}$) of the residue preceding Pro (or analog) and the carbon atom of the carbonyl group of Pro (or analog) $>C_i=O_i$.

[c] $\theta$ corresponds to the angle between $O_{i-1}$, $C_i$ and $O_i$.

**Table S4**. Dihedral angles of 5-substituted proline analogues in CSD.

| compound | abs. config. | hydrogen replaced | $\phi$ ° | $\psi$ ° | $\chi_2$ [a] ° | d [b] | $\theta$ [c] ° | CSD |
|---|---|---|---|---|---|---|---|---|
| **L-proline-*trans*** | | | | | | | | |
| Ac-(5OH-Pro)-Ome | 2S,5R | 5R | -72 | 160 | -38.6 | 3.09 | 94.3 | BOWHEA |
| Boc-(5CNPro)-Ome | 2S,5R | 5S | -57 | 145 | 36.5 | 2.90 | 93.3 | UDAQIB |
| Ac-(COOMe-Pro)-Ome | 2S,5R | 5S | -68 | 166 | 38.3 | 2.94 | 87.3 | GEBLAD |
| Bz-(5Mes-Pro)-Ome | 2S,5R | 5S | -54 | 144 | 34.2 | 2.83 | 98.8 | GODYAA |
| Ac-(5Me-Pro)-NHMe | 2S,5R | 5R | -66 | 152 | -38.9 | 3.01 | 97.6 | BIJFEF10 |
| Fm-(5Mes-Pro)-OH | 2S,5R | 5S | -57 | n.d. [b] | 30.5 | 2.88 | n.d. [b] | KENYEI |
| Boc-(5Cnp)-Ome | 2S,5S | 5R | -75 | 157 | -34.9 | 3.15 | 95.0 | UDAQEX |
| Ac-(5Me-Pro)-NHMe | 2S,5S | 5S | -65 | 150 | 36.7 | 2.93 | 95.9 | CEDROS |
| **D-proline-*trans*** | | | | | | | | |
| Ac-($CH_2$Ph-Pro)-OMe | 2R,5R | 5S | 62 | -160 | 38.2 | 2.89 | 92.3 | YOVXIS |
| Boc-(5-$CF_3$-Pro)-OMe | 2R,5S | 5R | 75 | -167 | -34.4 | 3.00 | 88.2 | UWILIX |
| **L-proline-*cis*** | | | | | | | | |
| $Ph_2$Carbamoyl-5-Azp-OMe | 2S,5S | 5S | -51 | -178 | 31.9 | 3.95 | 60.8 | ZIKNEM |
| Boc-((5-PhSO2-Pro-OEt | 2S,5R | 5R | -48 | 150 | -33.6 | 3.87 | 69.4 | VEXJAK |
| Bz-(($COO_2$Et)$_2$$CCH_3$)-Pro-Oet | 2S,5S | 5R | -46 | -32 | -31.4 | 4.03 | 147.5 | EHUTEG |
| Boc-(5-allyl)Pro-OtBu | 2S,5S | 5R | -57 | 162 | -37.9 | 4.17 | 73.7 | BAVZEE |
| Boc-(($^t$BuPh$_2$Si)Oet)Pro-H | 2S,5S | 5R | -49 | -37 | -24.4 | 4.11 | 138.3 | NEJKAO |
| Boc-(5$C_2H_4$OH-Pro)-OtBu | 2S,5S | 5R | -60 | 156 | -36.0 | 4.18 | 77.0 | OBAZUM |
| Boc-(5-(2-oxobutyl)Pro-OMe | 2S,5S | 5R | -56 | 153 | n.d. [d] | 4.13 | n.d. [d] | OVIMIR |
| CBz-(PhOHEt-Pro)-O$^t$Bu | 2S,5R | 5S | -77 | 180 | n.d. [d] | 4.17 | 74.5 | REMXOW |
| CBz-(PhOHEt-Pro)-O$^t$Bu | 2S,5S | 5R | -84 | -176 | -37.8 | 4.38 | 75.0 | REMXUC |
| Bz-((5-bisEthoxycarbonyl-methyl-Pro)-OEt | | | -113 | 153 | -32.2 | 4.63 | 95.9 | EHUTAC |
| **D-proline-*cis*** | | | | | | | | |
| X-(5-$CO_2$Me-Pro)-OMe | | | 63 | -163 | 38.3 | 4.20 | 75.5 | YEWKAM |

[a] The *exo* and *endo* ring puckers are shown in blue and red, respectively.

[b] 'd' corresponds to the distance (in Å) between carbonyl oxygen atom ($O_{i-1}$) of the residue preceding Pro (or analog) and the carbon atom of the carbonyl group of Pro (or analog) >$C_i$=$O_i$.

[c] $\theta$ corresponds to the angle between $O_{i-1}$, $C_i$ and $O_i$.

[d] n.d. = no data (due to disorder)