Descriptor	Elimination threshold
Total charge	< -3, > +3
Number of rotatable bonds	> 15
Number of heavy atoms	< 10
Molecular weight	< 150, > 650

The PDB IDs of the excluded structures after frequency analysis

4 times: 1PE, ASC, H35, MPO, NZ9, PEP, PHE

5 times: 017, BTB

6 times: PLM, SKM, TAR, ZEA

8 times: FLC

13 times: EPE, GSH, TLA

18 times: PG4

20 times: PGE

23 times: MES

26 times: CIT

PDB_ID(Complex)-PDB_ID(Ligand)

1d2s-DHT, 1adl-ACD, 1aoe-GW3, 1bk0-ACV, 1c1d-PHE, 1c1x-HFA, 1c5n-ESI, 1c5q-ESI, 1cil-ETS, 1df8-BTN, 1dry-AAG, 1dz4-CAM, 1dzk-PRZ, 1e6q-NTZ, 1e6s-GOX, 1e8m-P0H, 1ee2-CHD, 1elu-PDA, 1f8d-9AM, 1f8e-49A, 1fsg-9DG, 1ftk-KAI, 1g67-TZP, 1g6c-IFP, 1g6s-S3P, 1g6s-GPJ, 1gkl-FER, 1gm7-PNN, 1gtz-DHK, 1gvf-PGH, 1gvg-PCX, 1gz8-MBP, 1gzt-FUC, 1h00-FCP, 1h00-FAP, 1h46-RNP, 1hb1-OCV, 1hxk-DMJ, 1hy7-MBS, 1hyo-HBU, 1icm-MYR, 1ie8-KH1, 1ie9-VDX, 1j96-TES, 1ja9-PYQ, 1jd0-AZM, 1jtv-TES, 1jvp-LIG, 1k3l-GTX, 1kb0-PQQ, 1kei-LYS, 1kfc-IPL, 1kjo-THR, 1kjp-GLU, 1kkk-ASP, 1kqw-RTL, 1kvl-THN, 1kvl-CLS, 1kw6-BPY, 1kzk-JE2, 1ltz-HBI, 1m5e-AM1, 1mgo-PFB, 1mqd-SHI, 1mqi-FWD, 1n8v-BDD, 1n8v-BDD, 1n8v-BDD, 1nbu-PH2, 1nlu-TYB, 1nq7-ARL, 1o6f-SIN, 1o98-2PG, 1oaf-ASC, 1obn-ASV, 1odn-APV, 1oew-THR, 1of8-PEP, 1of8-G3P, 1oh0-EQU, 1ohp-ESR, 1oit-HDT, 1ow4-2AN, 1owe-675, 1phb-PFZ, 1phg-MYT, 1q11-TYE, 1q6o-LG6, 1qgu-HCA, 1qiq-ACC, 1qje-IP1, 1qxy-M2C, 1qzy-TDE, 1rb0-HH2, 1re9-DSO, 1sdt-MK1, 1snn-5RP, 1sqn-NDR, 1sv3-ANN, 1t46-STI, 1t7f-DHT, 1tf9-PHI, 1tjp-HPF, 1tjy-PAV, 1tkh-DPN, 1tzc-PA5, 1u0f-G6P, 1u0f-G6Q, 1u3w-FXY, 1uf5-CDT, 1uof-PNN, 1urw-I1P, 1uzw-CDH, 1w04-HCG, 1w3v-MDZ, 1w3x-W2X, 1w6s-PQQ, 1wb4-SXX, 1wb6-VXX, 1wbi-BTN, 1wbj-G3P, 1x9h-F6R, 1x9i-G6Q, 1xbb-STI, 1xg4-ICT, 1xic-XLS, 1xom-CIO, 1xoz-CIA, 1xpc-AIT, 1y2b-DEE, 1y2k-7DE, 1y3v-UIR, 1y5v-NE8, 1y5w-NEZ, 1y9l-UND, 1yvm-TMG, 1zdy-T3A, 1zhx-HC3, 1zhy-CLR, 1zz1-SHH, 2ad6-PQQ, 2afw-AHN, 2aib-ERG, 2al1-PEP, 2al1-2PG, 2ax6-HFT, 2bju-IH4, 2bju-IH4, 2bkx-F6R, 2brc-CT5, 2bu9-HFV, 2bvr-4CP, 2bz6-346, 2c2n-AE4, 2c4j-GSO, 2c92-TP6, 2cle-F6F, 2clk-G3H, 2cll-PLS, 2cll-F9F, 2clo-F19, 2ctc-HFA, 2cxq-S6P, 2d5x-L35, 2d5z-L35, 2d5z-L35, 2de3-OBP, 2dqm-BES, 2ecu-1PG, 2ei0-BP7, 2ei0-BP7, 2ei1-D1N, 2ej0-PMP, 2eu3-FF3, 2f01-BTQ, 2f18-GB1, 2f1a-GB2, 2f1b-GB3, 2f7o-MSN, 2f7p-2SK, 2f7r-SK3, 2fhl-BNI, 2fmg-PHE, 2fmz-DPN, 2gu5-NLP, 2gyi-HYA, 2h7j-H7J, 2hai-PFI, 2hhn-GNQ, 2hzy-DHJ, 2i4u-DJR, 2ica-2IC, 2ikg-BTO, 2ikh-LIT, 2imd-2C2, 2imd-TOH, 2iog-IOG, 2ivi-ACW, 2ivj-BCV, 2izr-BRK, 2j5s-KTA, 2jb4-A14, 2jkb-SKD, 2nmx-M25, 2nnd-PRZ, 2nq6-HM4, 2nq7-HM5, 2nqz-PRF, 2nvd-ITB, 2nwr-PEP, 2o2c-G6Q, 2os1-BB2, 2pdg-47D, 2piy-528, 2piz-606, 2pou-I7A, 2pov-I7B, 2pqz-G0G, 2pr3-237, 2puj-HPZ, 2pw0-TRC, 2pwr-G4G, 2qci-65, 2qp6-MB1, 2qp8-SC7, 2qwc-DAN, 2qyn-NPV, 2qzz-EMF, 2r3f-SC8, 2r3g-SC9, 2r3h-SCE, 2r3r-6SC, 2r43-G3G, 2r8q-IBM, 2rbs-269, 2rct-RTL, 2rdn-1PL, 2rhw-C0E, 2rkv-MPO, 2sim-DAN, 2uy5-H35, 2v00-V15, 2v3i-XX6, 2v3r-XX7, 2v6k-TGG, 2vb8-TLM, 2vbp-VB1, 2vij-C44, 2viz-VG4, 2vj7-VG6, 2vj9-VG7, 2vk2-GZL, 2vro-ETE, 2vuk-P83, 2w09-CM9, 2w0a-CII, 2w0b-CMW, 2w3b-VG9, 2w9h-TOP, 2wbo-ARG, 2wcj-M21, 2wcm-B9M, 2wd4-TBV, 2wec-PP5, 2weg-FBV, 2wej-FB2, 2weo-FBW, 2wer-RDC, 2wf0-ZY0, 2wf1-ZY1, 2wf8-BG6, 2whf-II4, 2whf-II4, 2wsa-646, 2wxd-E18, 2x5w-K2B, 2xf3-J01, 2xf3-J01, 2xir-00J, 2xts-MTE, 2xx8-1NE, 2xxh-1NG, 2xxi-JAC, 2y60-M8F, 2y6d-TQJ, 2yc3-MW5, 2yc5-6BC, 2ydi-YDI, 2yld-ASC, 2z7k-BGU, 2zgb-21U, 2znt-DYH, 2zq2-13U, 2zxg-S23, 2zya-6PG, 2zyd-GLO, 3a40-23R, 3acx-673, 3akn-11D, 3arp-DEQ, 3arx-POY, 3arx-POY, 3az1-DS2, 3az3-DS6, 3b0t-MCZ, 3b34-PHE, 3b7e-ZMR, 3bc9-GLC, 3bex-PAU, 3bhy-7CP, 3blb-SWA, 3bll-BPQ, 3blo-QEI, 3bmx-P4G, 3bmy-CXZ, 3bp1-GUN, 3bqc-EMO, 3bxs-DRS, 3bxs-DRS, 3c2u-B3P, 3cen-FXA, 3cfb-SPB, 3cmj-SRT, 3cse-N22, 3czy-AD8, 3d4y-MVL, 3d51-GOX, 3d52-GHR, 3d78-NBB, 3d7f-YBY, 3d7h-YC2, 3d80-Q22,

3d97-B3P, 3ddf-GB6, 3ddu-552, 3dgq-EAA, 3dha-C6L, 3dhc-CYK, 3dj8-EXY, 3djk-G55, 3dn5-53N, 3dsi-T24, 3dsj-243, 3dsk-T25, 3dux-64U, 3dx2-MZB, 3dx4-GOO, 3eck-XXG, 3ei8-PL5, 3ejp-HN2, 3ejq-HN3, 3ejr-HN4, 3ejs-HN5, 3ejt-HN6, 3eju-HN7, 3eko-PYU, 3eq0-2TS, 3f0u-53R, 3f80-6HN, 3f9m-MRK, 3fed-BIX, 3ffg-FFG, 3fgd-BYA, 3fuc-9DG, 3fun-798, 3fv2-NDZ, 3fvg-MS8, 3fvk-8DX, 3fvn-9DX, 3fvo-8EP, 3g5h-YTT, 3gba-DYH, 3gc5-2MQ, 3ge7-AFQ, 3gen-B43, 3ghc-GHC, 3ghw-GHW, 3gkn-BIH, 3goc-YES, 3gp3-SEP, 3gp6-SDS, 3gp6-SDS, 3gt3-BRV, 3gus-N11, 3gzx-BNL, 3h1x-IMN, 3h61-ENL, 3h8g-BES, 3hcn-CHD, 3hcn-CHD, 3hf5-3ML, 3hp9-CF1, 3huk-J0Z, 3i6c-GIA, 3i6o-GR6, 3ib0-DIF, 3iji-DGL, 3ijl-DGL, 3ip8-B85, 3itu-IBM, 3itv-PSJ, 3iu7-FCD, 3ix3-OHN, 3jum-AOD, 3jyp-QIC, 3k1w-BFX, 3k5x-P8D, 3kbn-GLO, 3kdm-TES, 3kfa-B91, 3kgc-ZK1, 3kgc-LY7, 3ki0-G9D, 3ki1-G9F, 3ki2-G9G, 3ki3-G9H, 3ki5-G9M, 3ki6-G9L, 3ki7-G9I, 3kig-DA4, 3kv2-NNH, 3kx1-KX1, 3l3x-DHT, 3l5e-BDW, 3ljj-10U, 3ljo-11U, 3ly0-LY0, 3m0h-RNS, 3m0j-OAF, 3m0m-AOS, 3m2y-BE0, 3m40-J45, 3m8t-4NZ, 3m98-E02, 3mdu-NGQ, 3mfw-B3U, 3mhw-ABV, 3myq-E27, 3mzc-S6I, 3n0n-P9B, 3n4b-WWZ, 3nhi-EAH, 3nht-U46, 3nnt-DQA, 3ntz-3TZ, 3nu0-3TU, 3nvs-S3P, 3nvs-GPJ, 3nxo-D2B, 3nxx-D2D, 3nz1-3NY, 3nzb-D2N, 3o5l-1PE, 3o9b-K2A, 3o9e-A60, 3o9i-A61, 3ogn-3OG, 3oig-IMJ, 3ok9-G52, 3oq6-PFB, 3ot3-22K, 3ovv-1SB, 3oy0-OY0, 3oyq-OYQ, 3oys-OYS, 3ozm-LY9, 3ozm-DXL, 3p17-99P, 3p6d-ZGB, 3p6e-ZGC, 3p6f-FBZ, 3p6g-IZP, 3p6h-IBP, 3pa3-C70, 3pa4-C72, 3pc3-P1T, 3pcw-FBF, 3pe1-3NG, 3pfb-ZYC, 3pkb-Y16, 3pkc-Y08, 3pkd-Y10, 3pld-F90, 3pmu-F7L, 3pmy-41L, 3poo-S69, 3poz-03P, 3prs-1PE, 3psy-RB9, 3psy-1PE, 3pyx-12T, 3q0w-LL5, 3q6y-S47, 3qaa-G04, 3qih-FG7, 3qih-NI7, 3qke-GCO, 3ql0-FOL, 3qp0-NI8, 3qp1-HL6, 3qp4-HL0, 3qrs-NK8, 3qyk-IE2, 3r16-5UN, 3r92-06J, 3rbu-G88, 3rly-S29, 3rm0-S54, 3rm6-18Z, 3rml-M31, 3rmm-M32, 3ryj-RYJ, 3ryv-RYV, 3ryx-RYX, 3ryy-RYY, 3s0e-EOL, 3s2j-L3A, 3s2l-LDE, 3s2m-P5D, 3s2n-P4D, 3s72-EVE, 3s74-03T, 3s8x-BCN, 3sa7-55A, 3sa8-K83, 3sab-F78, 3sac-AF8, 3san-ZMR, 3sbf-D8T, 3sbi-E90, 3sha-P97, 3sm0-AEK, 3sqy-Q11, 3szl-H6P, 3t44-IGP, 3t4s-H35, 3t5f-M34, 3t6i-Z82, 3tao-PGH, 3tcy-PHE, 3th9-9Y9, 3ti8-LNV, 3tkd-CYZ, 3tki-S25, 3tog-79, 3tpp-5HA, 3u98-BJA, 3u9q-DKA, 3u9w-28P, 3ucc-2PG, 3ucd-PEP, 3up0-D7S, 3up3-XCA, 3upe-0CA, 3uqi-MPO, 3urk-0CG, 3uv3-0CM, 3uv7-0CN, 3v7x-D7A, 3v9v-21L, 3veu-0GO, 3vf3-0GS, 3vgn-FNN, 3vhd-VHE, 3vhe-42Q, 3vhv-LD1, 3vif-LGC, 3vig-NOJ, 3vk5-FPQ, 3vmk-IPM, 3vo3-0KF, 3vq8-BCU, 3vri-1KX, 3vtc-TK3, 3vxi-ASC, 3vxj-3DM, 3wfg-WFG, 3wvs-RRM, 3wx9-3EE, 3zcl-5TF, 3zkq-B3P, 3zku-HCV, 3zky-WT4, 3zou-6H6, 3zou-GPP, 3zxh-E41, 3zzs-TRP, 4a39-GEM, 4a7g-12I, 4a7u-ALE, 4a7v-LDP, 4a83-DXC, 4a85-H35, 4a86-H35, 4agm-P86, 4avs-N7P, 4awq-592, 4ayq-MVL, 4ayr-IFL, 4ayr-IFL, 4b11-7I1, 4b13-X25, 4b14-4XB, 4b70-WM9, 4b72-2FB, 4b78-KGG, 4bb3-KKA, 4bcd-TDV, 4bcw-TU0, 4bgu-1PE, 4bmn-TAM, 4bue-JQF, 4bw1-S5B, 4c1c-MCO, 4c1e-MCO, 4c38-VUP, 4c72-TLG, 4cae-3F3, 4cgl-A6K, 4cgo-6KV, 4cgo-6KV, 4cpf-LH3, 4cyo-UEK, 4dgr-3LV, 4di9-0GY, 4djr-0KJ, 4djx-0KQ, 4do4-DJN, 4do5-DGJ, 4don-3PF, 4drm-0MC, 4dtz-LDP, 4dz7-D02, 4dz9-ID4, 4e3d-GTQ, 4e3f-GRE, 4e4a-JKE, 4egh-0OY, 4ehv-0SJ, 4ehv-0SJ, 4ek5-03K, 4ek6-10K, 4ew2-DXY, 4ey2-0RM, 4eyb-0WO, 4fkg-4CK, 4fkl-CK2, 4fko-20K, 4flg-ILE, 4fli-Y16, 4flk-Y10, 4fll-YZ6, 4fm7-0UP, 4fmx-CNL, 4fps-0UX, 4g1q-T27, 4g1x-TQU, 4g1x-TQU, 4g44-TZM, 4g45-MQN, 4g46-TTY, 4g47-TZF, 4g48-PZB, 4g8b-HL6, 4g9e-C4L, 4gcj-X64, 4gd9-BTN, 4ger-LYS, 4gg9-0WW, 4ghe-4NC, 4ghg-DHY, 4gkt-0O1, 4gv1-0XZ, 4h3j-10W, 4h4d-10E, 4h6b-10X, 4h6b-10Y, 4hct-18R, 4hdb-G52, 4hg9-G3P, 4hjl-15O, 4hlc-T05, 4hry-TAM, 4ht2-V50, 4ht2-V50,

4huo-RS8, 4hxn-1A7, 4hy4-1BG, 4hyi-1AO, 4hzm-1BW, 4hzz-G39, 4i00-ZMR, 4i3b-BLA, 4i3g-MPO, 4i7t-1DW, 4ibg-1D6, 4ibj-1D9, 4igt-3ZA, 4ikt-TFV, 4iku-SHX, 4ilx-1EZ, 4inw-1EY, 4ips-1G4, 4ipw-1G7, 4itu-1HS, 4ivt-VTI, 4ixe-IXE, 4j5h-1K4, 4j7n-9MG, 4ja8-1K9, 4jej-1GP, 4jew-P00, 4jey-PLP, 4jfj-1KU, 4jfk-JFK, 4jfl-1KY, 4jfm-1KZ, 4jh7-1KM, 4jht-8XQ, 4jmb-1LW, 4jpt-Q24, 4jq1-NPS, 4jq4-IMN, 4jqa-ID8, 4jtq-FLP, 4jtr-IZP, 4jtr-IBP, 4jv8-1M1, 4jze-1NK, 4k60-1P8, 4k9g-1Q2, 4kae-TGG, 4kap-1QV, 4keb-1QZ, 4kfg-DOO, 4kfn-1QR, 4kfo-1QS, 4klv-KLV, 4kmv-T6C, 4knn-E1F, 4kor-4KR, 4kot-CE3, 4kp6-1S1, 4ks7-X4Z, 4ktj-KTJ, 4ktk-KTK, 4kz4-4A1, 4kz5-1U3, 4kz7-1U5, 4kza-NZ9, 4kza-NZ9, 4kza-NZ9, 4kza-NZ9, 4kzb-NZ2, 4kzb-NZ3, 4kzb-NZ2, 4kzb-NZ2, 4l6b-1VS, 4l7g-1W0, 4l9p-FII, 4lge-1Y0, 4lhi-WWL, 4lls-IPE, 4llt-IPE, 4lrq-MPO, 4lva-20M, 4lvf-20P, 4lwe-FJ2, 4lwg-FJ4, 4lz5-1YV, 4m14-QWS, 4m14-QWS, 4m5r-MSR, 4mc1-526, 4mc2-525, 4mc3-28U, 4mc6-23K, 4mc9-23L, 4mmm-BP7, 4mnc-173, 4mrh-2CQ, 4mry-CEI, 4mrz-2ZV, 4myd-164, 4n6k-X3X, 4nfn-2KC, 4nn3-ORO, 4nog-PLP, 4ntk-ZSP, 4o10-2QF, 4o71-CPB, 4oba-2TW, 4og6-2S9, 4ohu-2TK, 4otq-2V2, 4p4c-25Q, 4p5q-Q0B, 4p7x-CXS, 4pdy-HIS, 4psb-GA3, 4pyq-2X1, 4q4o-2YM, 4q4r-SQO, 4qf7-C0R, 4qte-390, 4tvt-ASC, 4u21-FWF, 4ua4-3C7, 7atj-FER

Table S1. Variation of molecular weight (MW) and number of heavy atoms (#HA) for different ranges of rotatable bond counts.

MW	% in #ROTB 0-3	MW	% in #ROTB 4-6	MW	% in #ROTB 7-10	MW	% in #ROTB 10-15
150 – 250	67	150 – 250	36	150 – 250	16	150 – 250	20
250 – 350	23	250 – 350	33	250 – 350	27	250 – 350	29
350 – 450	10	350 – 450	25	350 – 450	27	350 – 450	14
450 – 650	0	450 – 650	6	450 – 650	30	450 – 650	37
#HA	**% in #ROTB 0-3**	**#HA**	**% in #ROTB 4-6**	**#HA**	**% in #ROTB 7-10**	**#HA**	**% in #ROTB 10-15**
10 – 15	57	10 – 15	28	10 – 15	11	10 – 15	11
15 – 20	21	15 – 20	23	15 – 20	15	15 – 20	31
20 – 25	16	20 – 25	23	20 – 25	22	20 – 25	11
25 – 30	5	25 – 30	18	25 – 30	18	25 – 30	6
>30	1	>30	8	>30	34	>30	40

Table S2. Variation of number of rotatable bonds (#ROTB) and number of heavy atoms (#HA) for different ranges of molecular weight (MW).

#HA	% in MW 150-250	#HA	% in MW 250-350	#HA	% in MW 350-450	#HA	% in MW 450-650
10 – 15	78	10 – 15	4	10 – 15	0	10 – 15	0
15 – 20	22	15 – 20	40	15 – 20	1	15 – 20	0
20 – 25	0	20 – 25	56	20 – 25	26	20 – 25	1
25 – 30	0	25 – 30	0	25 – 30	62	25 – 30	3
>30	0	>30	0	>30	11	>30	96
#ROTB	**% in MW 150-250**	**#ROTB**	**% in MW 250-350**	**#ROTB**	**% in MW 350-450**	**#ROTB**	**% in MW 450-650**
≤ 4	76	≤ 4	47	≤ 4	34	≤ 4	2
≤ 7	17	≤ 7	33	≤ 7	37	≤ 7	23
≤ 10	5	≤ 10	11	≤ 10	15	≤ 10	33
≤ 15	3	≤ 15	10	≤ 15	14	≤ 15	43

Table S3. Increase of RMSD according to the number of charged groups on ligands (CHARGED INPUT).

#charged groups	total#comps	RMSD per comp. OPLS2005-chloroform	RMSD per comp. MMFFs-chloroform	RMSD per comp. OPLS3-chloroform	RMSD per comp. AMBER-chloroform
1	328	0.79	0.78	0.77	0.78
2	112	1.03	1.08	0.97	1.03
3	62	1.64	1.64	1.49	1.63
4-5	15	1.51	1.64	1.42	1.56
#charged groups	**total#comps**	**RMSD per comp. OPLS2005-octanol**	**RMSD per comp. MMFFs-octanol**	**RMSD per comp. OPLS3-octanol**	**RMSD per comp. AMBER-octanol**
1	328	0.75	0.73	0.72	0.79
2	112	1.00	0.97	0.88	1.05
3	62	1.52	1.55	1.43	1.57
4-5	15	1.50	1.57	1.38	1.51
#charged groups	**total#comps**	**RMSD per comp. OPLS2005-water**	**RMSD per comp. MMFFs-water**	**RMSD per comp. OPLS3-water**	**RMSD per comp. AMBER-water**
1	328	0.64	0.62	0.59	0.65
2	112	0.79	0.79	0.69	0.72
3	62	1.29	1.28	0.97	0.87
4-5	15	1.40	1.20	1.11	1.15

Table S4. Increase of RMSD according to the number of charged groups on ligands (NEUTRALIZED INPUT).

#charged groups	total#comps	RMSD per comp. OPLS2005-chloroform	RMSD per comp. MMFFs-chloroform	RMSD per comp. OPLS3-chloroform	RMSD per comp. AMBER-chloroform
1	328	0.66	0.66	0.68	0.69
2	112	0.82	0.83	0.83	0.83
3	62	1.15	1.12	1.01	1.01
4-5	15	1.25	1.09	1.25	1.12
#charged groups	**total#comps**	**RMSD per comp. OPLS2005-octanol**	**RMSD per comp. MMFFs-octanol**	**RMSD per comp. OPLS3-octanol**	**RMSD per comp. AMBER-octanol**
1	328	0.64	0.63	0.65	0.67
2	112	0.78	0.78	0.76	0.89
3	62	0.94	1.00	1.01	0.87
4-5	15	1.13	1.04	1.13	0.98
#charged groups	**total#comps**	**RMSD per comp. OPLS2005-water**	**RMSD per comp. MMFFs-water**	**RMSD per comp. OPLS3-water**	**RMSD per comp. AMBER-water**
1	328	0.59	0.56	0.58	0.63
2	112	0.73	0.70	0.73	0.79
3	62	0.71	0.78	0.74	0.78
4-5	15	0.91	0.77	0.89	0.85

Table S5. Sum of minimum RMSDs (Å) of all ligands divided by total number of ligands (809) for all force field-solvent pairs (2nd, 3rd, 4th columns), improvement of RMSD in Ångström (5th column), improvement of RMSD in percentage (6th column).

Force field	Charged (Å)	Neutralized (Å)	Combined (Å)	Difference (Å) (Charged − Combined)	% improvement (Charged − Combined)
OPLS2005-chloroform	0.841	0.719	0.672	0.168	20.0
OPLS2005-octanol	0.803	0.683	0.640	0.163	20.3
OPLS2005-water	0.717	0.630	0.585	0.132	18.4
MMFFs-chloroform	0.858	0.727	0.681	0.177	20.7
MMFFs-octanol	0.807	0.686	0.639	0.168	20.8
MMFFs-water	0.709	0.623	0.583	0.127	17.9
AMBER-chloroform	0.859	0.737	0.687	0.172	20.0
AMBER-octanol	0.862	0.730	0.690	0.173	20.0
AMBER-water	0.698	0.688	0.629	0.069	9.8
OPLS3-chloroform	0.818	0.721	0.662	0.156	19.1
OPLS3-octanol	0.767	0.680	0.629	0.138	18.0
OPLS3-water	0.636	0.608	0.543	0.093	14.6

Table S6. Results of the statistical analysis of RMSD increase per rotatable-bond for all force field-solvent combinations.

#ROTB –>	0		1		2		3		4		5		6	
OPLS2005-chloroform	4.86	0.14	21.66	0.14	23.94	0.14	50.91	0.13	83.92	0.13	68.04	0.13	72.09	0.13
OPLS2005-octanol	4.98	0.15	21.58	0.14	24.39	0.14	48.46	0.13	77.68	0.12	62.21	0.12	70.78	0.13
OPLS2005-water	4.80	0.14	21.94	0.14	27.20	0.15	46.79	0.12	79.37	0.12	58.34	0.11	56.40	0.10
MMFFs-chloroform	4.00	0.12	21.11	0.14	24.68	0.14	50.69	0.13	82.31	0.13	68.43	0.13	75.79	0.14
MMFFs-octanol	3.94	0.12	20.20	0.13	23.10	0.13	47.62	0.13	74.27	0.11	62.60	0.12	72.55	0.13
MMFFs-water	4.39	0.13	20.71	0.13	23.50	0.13	47.75	0.13	71.58	0.11	56.17	0.11	60.13	0.11
OPLS3-chloroform	4.45	0.13	21.06	0.14	22.12	0.12	50.12	0.13	78.69	0.12	62.77	0.12	69.53	0.13
OPLS3-octanol	4.44	0.13	20.31	0.13	19.07	0.11	46.65	0.12	71.14	0.11	55.39	0.11	62.76	0.12
OPLS3-water	4.67	0.14	20.15	0.13	20.93	0.12	39.60	0.10	61.60	0.09	49.49	0.09	51.68	0.10
OPLS3-gas	4.54	0.13	20.86	0.14	20.79	0.12	54.53	0.14	86.43	0.13	75.85	0.15	82.60	0.15
AMBER-chloroform	4.15	0.12	21.09	0.14	23.19	0.13	50.02	0.13	85.88	0.13	65.22	0.12	74.12	0.14
AMBER-octanol	4.12	0.12	20.76	0.13	23.45	0.13	46.86	0.12	78.12	0.12	65.89	0.13	76.20	0.14
AMBER-water	3.97	0.12	20.45	0.13	23.84	0.13	39.76	0.10	68.43	0.10	59.70	0.11	56.03	0.10
Explicit-water	6.93	0.20	27.04	0.18	22.90	0.13	47.85	0.13	85.36	0.13	64.27	0.12	68.97	0.13
BABEL-MMFFs	25.05	0.74	80.34	0.52	46.73	0.26	71.43	0.19	130.47	0.20	100.39	0.19	97.45	0.18
# Compounds	34		77		59		95		131		87		77	

Table S6. (Cont'd)

#ROTB –>	7		8		9		10		>11		RMSD-sum	
OPLS2005-chloroform	54.53	0.15	66.58	0.14	39.47	0.13	28.65	0.14	165.56	0.14	680.21	0.84
OPLS2005-octanol	50.53	0.13	59.90	0.13	40.72	0.14	23.60	0.12	164.50	0.13	649.33	0.80
OPLS2005-water	41.29	0.11	47.97	0.10	33.28	0.11	20.98	0.11	141.32	0.12	579.68	0.72
MMFFs-chloroform	55.28	0.15	69.46	0.15	40.61	0.14	27.19	0.14	174.67	0.14	694.22	0.86
MMFFs-octanol	51.06	0.14	61.89	0.13	39.73	0.13	25.38	0.13	170.23	0.14	652.57	0.81
MMFFs-water	41.13	0.11	48.27	0.10	32.32	0.11	22.31	0.11	145.60	0.12	573.86	0.71
OPLS3-chloroform	52.25	0.14	63.11	0.13	41.72	0.14	28.23	0.14	168.00	0.14	662.05	0.82
OPLS3-octanol	49.70	0.13	59.40	0.13	40.34	0.13	24.62	0.12	166.42	0.14	620.24	0.77
OPLS3-water	37.43	0.10	47.21	0.10	33.09	0.11	17.46	0.09	131.16	0.11	514.47	0.64
OPLS3-gas	61.57	0.16	73.37	0.16	49.27	0.16	29.52	0.15	195.27	0.16	754.60	0.93
AMBER-chloroform	55.37	0.15	63.83	0.14	43.32	0.14	27.32	0.14	181.32	0.15	694.83	0.86
AMBER-octanol	54.53	0.15	63.69	0.14	45.65	0.15	27.29	0.14	190.90	0.16	697.46	0.86
AMBER-water	45.39	0.12	50.99	0.11	36.11	0.12	22.79	0.12	137.37	0.11	564.83	0.70
Explicit-water	46.83	0.12	61.38	0.13	37.03	0.12	22.98	0.12	154.75	0.13	646.29	0.80
BABEL-MMFFs	66.88	0.18	72.76	0.16	48.57	0.16	34.15	0.17	180.05	0.15	954.27	1.18
# Compounds	47		52		30		18		102		809	

Table S7. Fraction of the ligands (%) that have the bioactive pose within the stated RMSD ranges (first column) from the global minimum structure.

RMSD	AMBER Chloroform	AMBER Octanol	AMBER Water	MMFFs Chloroform	MMFFs Octanol	MMFFs Water	OPLS3 Chloroform	OPLS3 Octanol	OPLS3 Water	OPLS2005 Chloroform	OPLS2005 Octanol	OPLS2005 Water
0.0 – 0.5	15.8	15.7	17.4	16.4	15.3	16.2	13.7	14.7	17.6	15.1	15.1	16.8
0.5 – 1.0	14.7	14.7	15.3	14.7	15.3	19.4	17.3	16.9	17.6	16.3	15.1	17.9
1.0 – 1.5	20.6	21.1	22.0	22.2	21.0	21.1	21.4	21.1	21.9	23.0	22.4	23.2
1.5 – 2.0	17.6	17.7	15.8	18.0	18.8	16.7	19.7	17.8	16.4	17.6	19.3	15.5
2.0 – 3.0	19.8	18.9	17.1	20.5	20.1	18.5	18.7	17.2	16.4	17.7	18.0	17.4
> 3.0	11.5	11.9	12.4	8.0	9.4	8.0	9.3	12.2	10.1	10.4	10.1	9.1

Best achieved RMSDs (most similar conformer to the crystal-pose) for ligands grouped by various descriptors (OPLS3 force field).

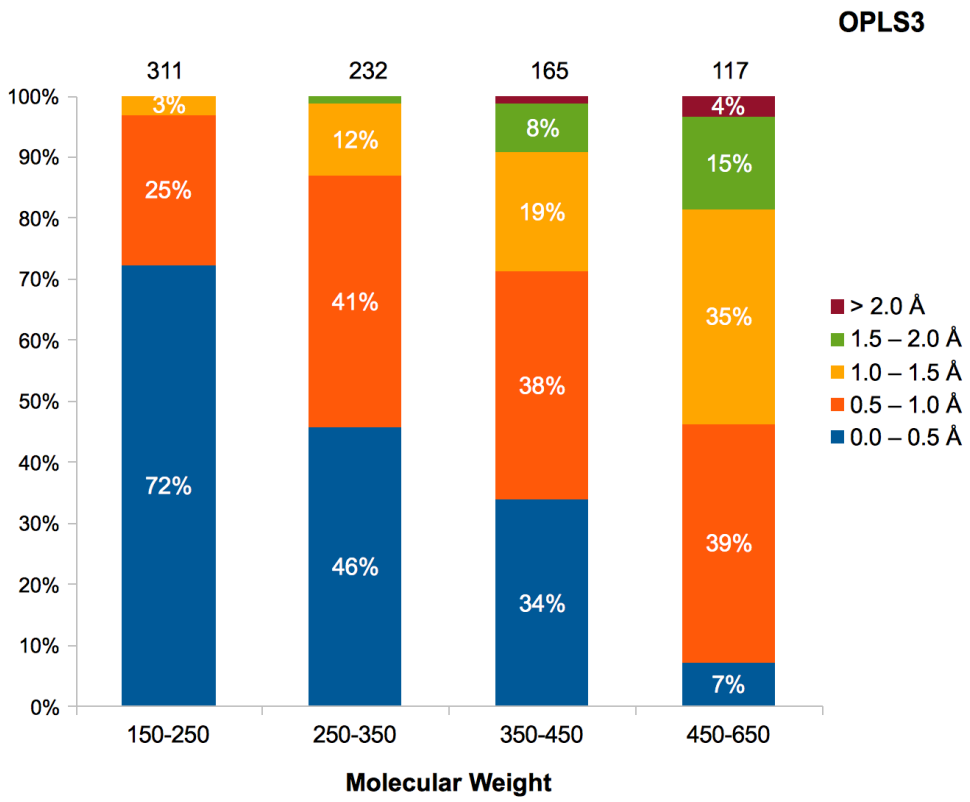

Figure S1

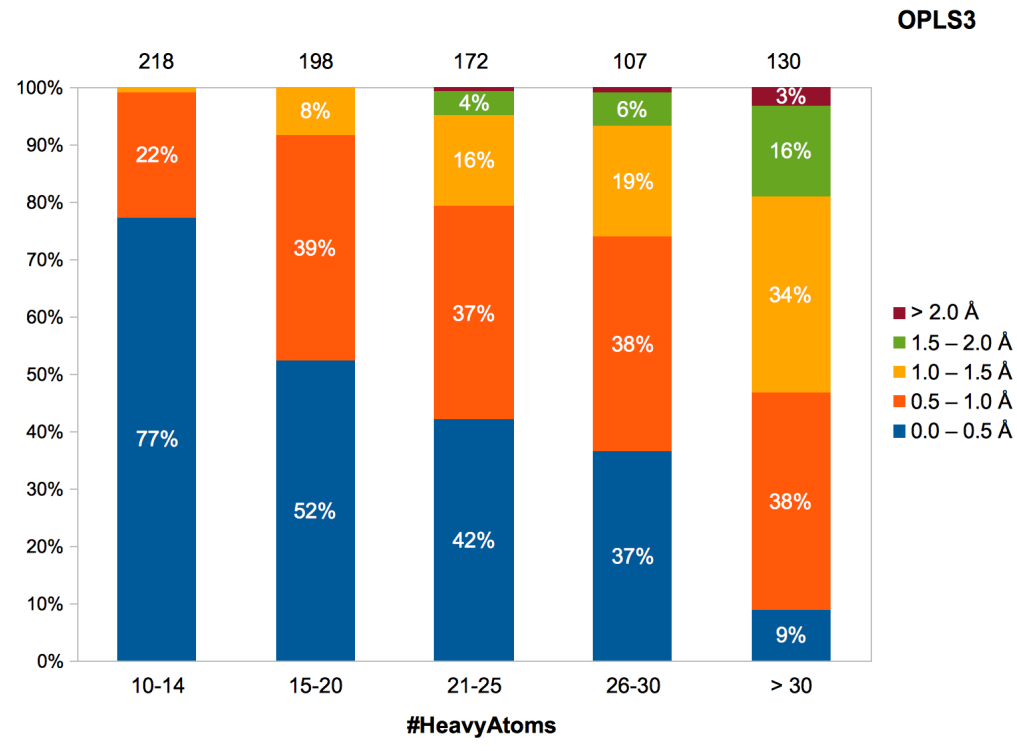

Figure S2

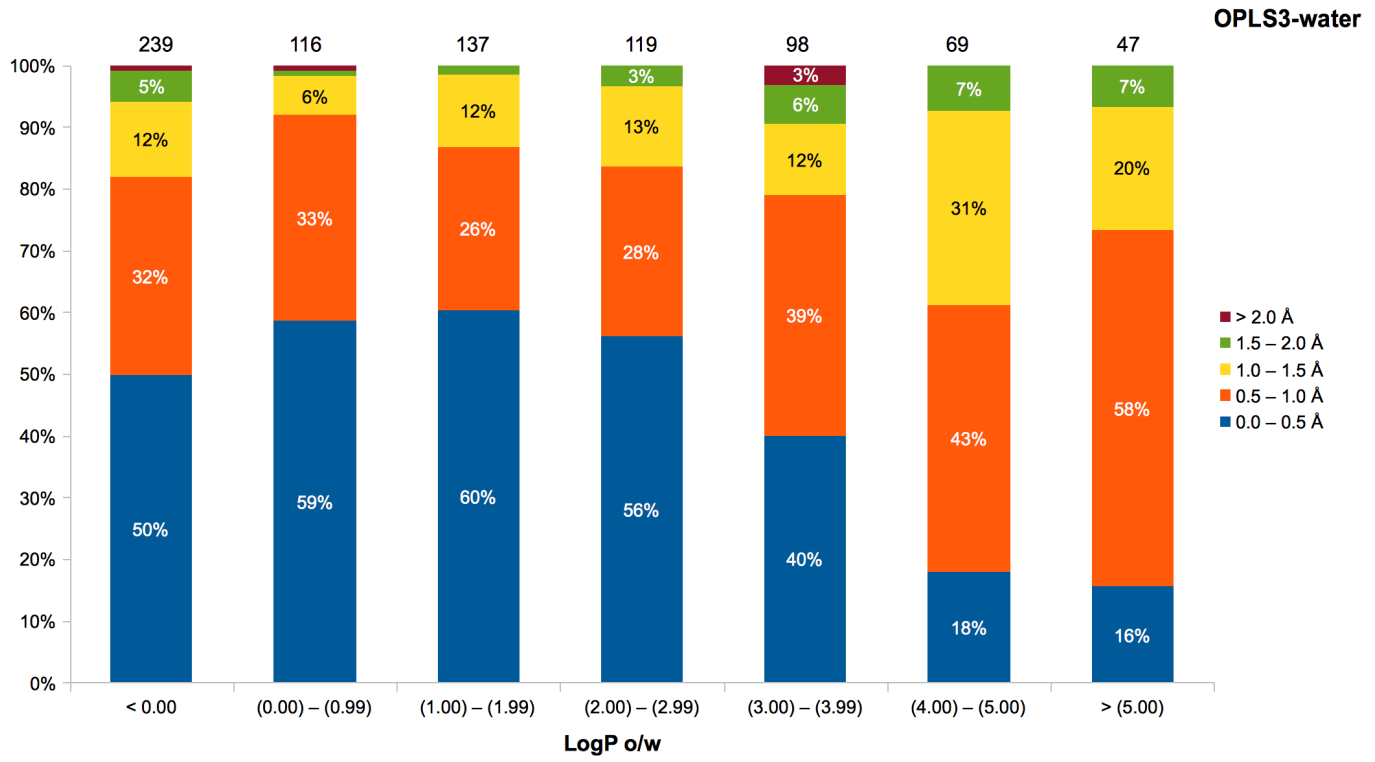

Figure S3

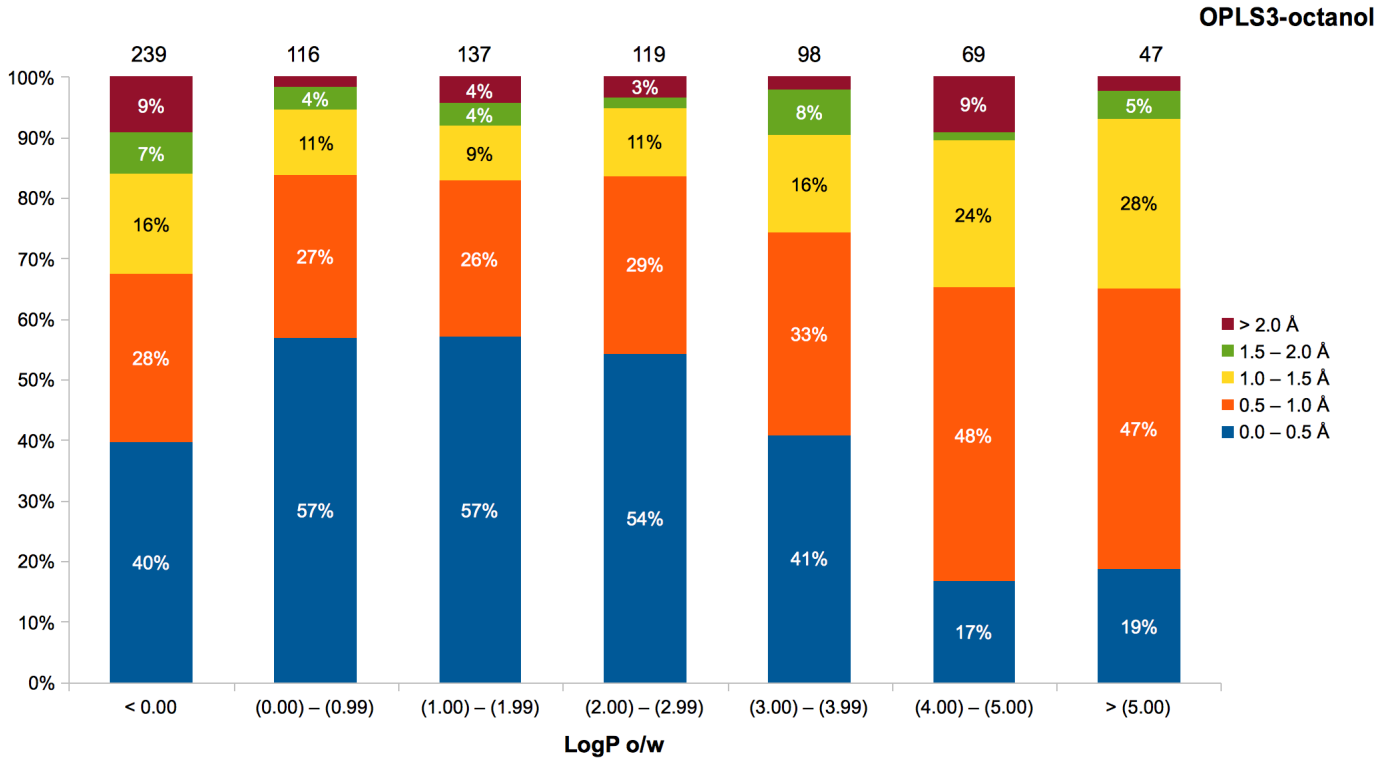

Figure S4

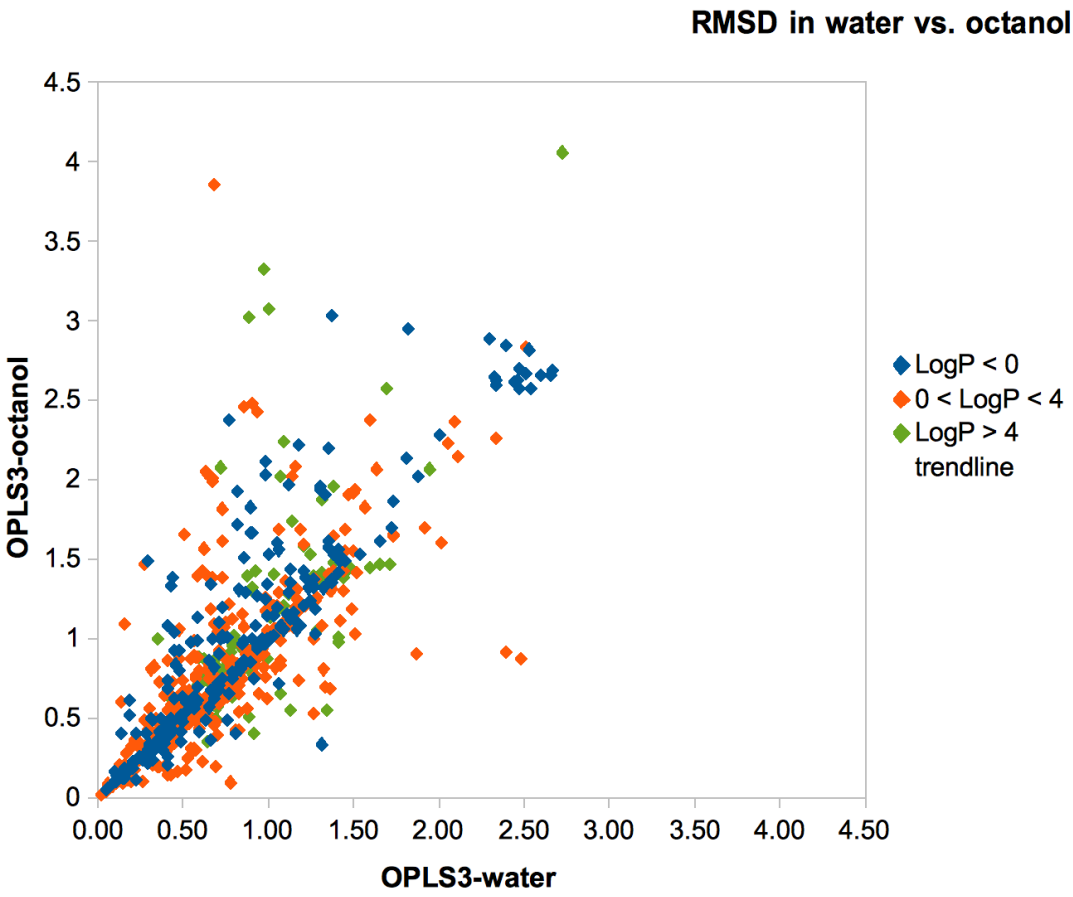

Figure S5

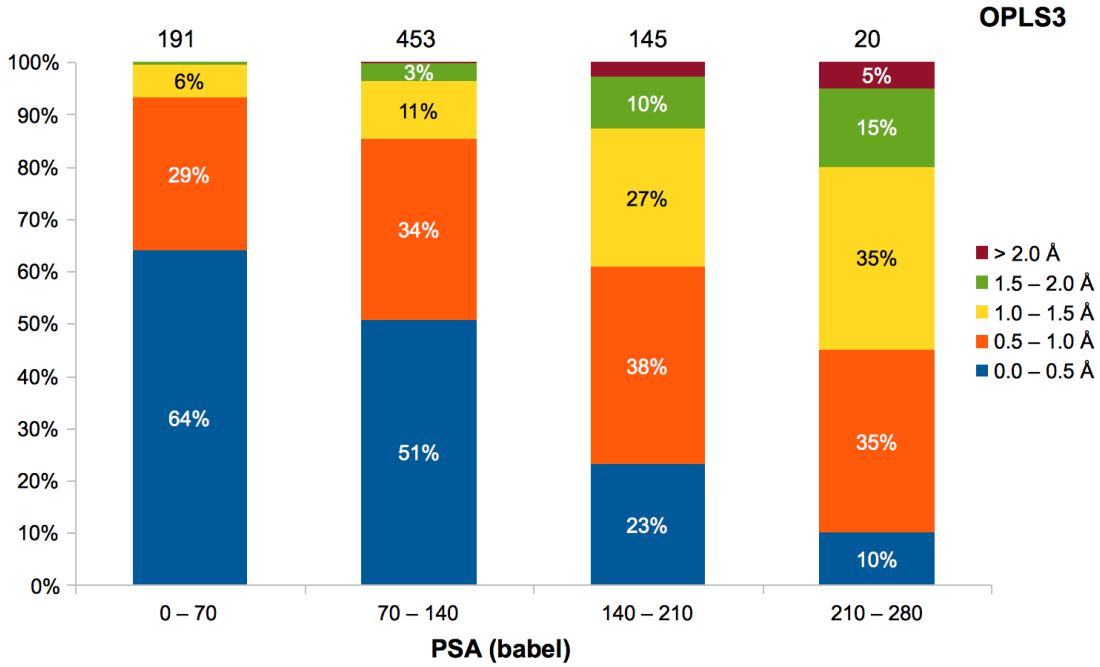

Figure S6

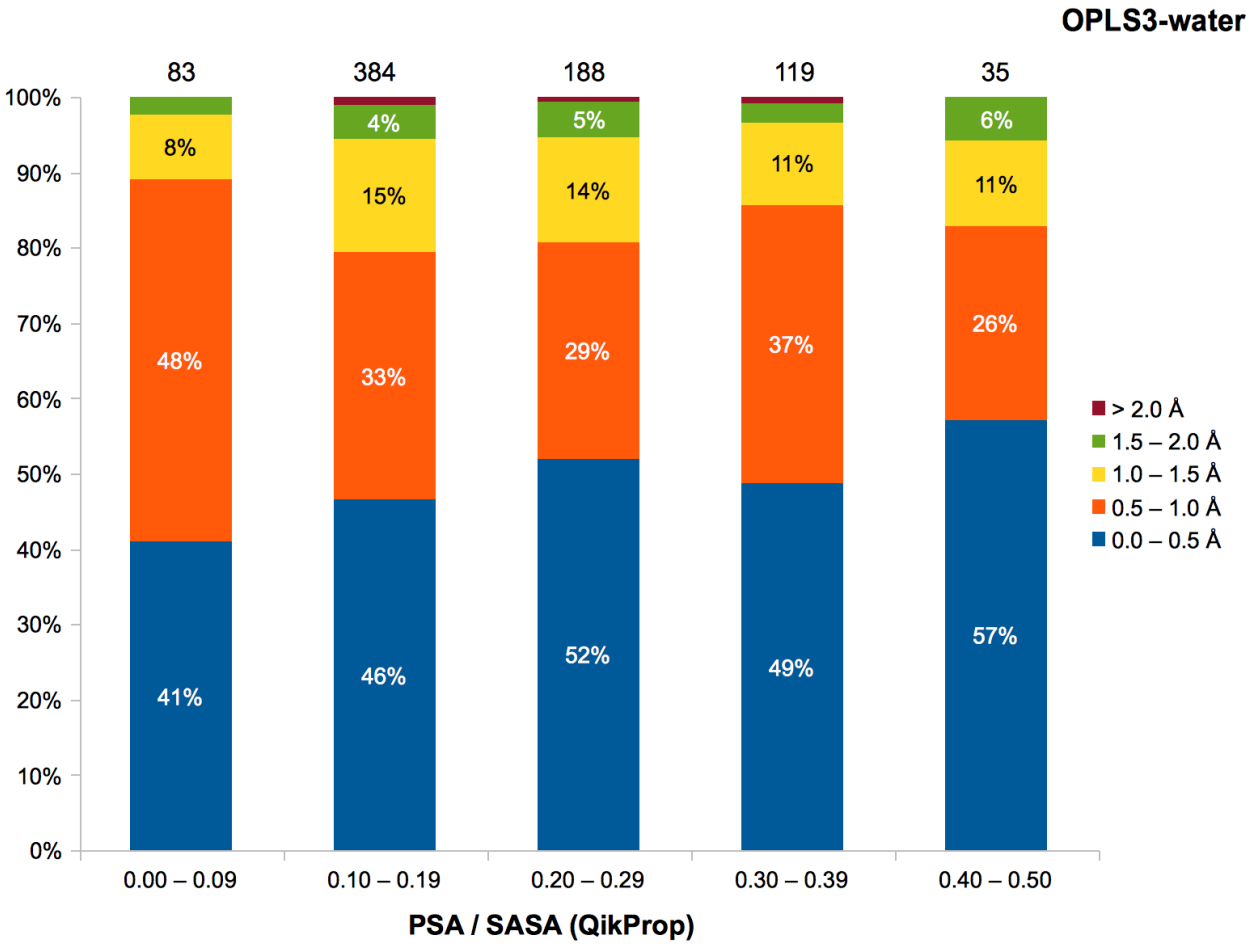

Figure S7

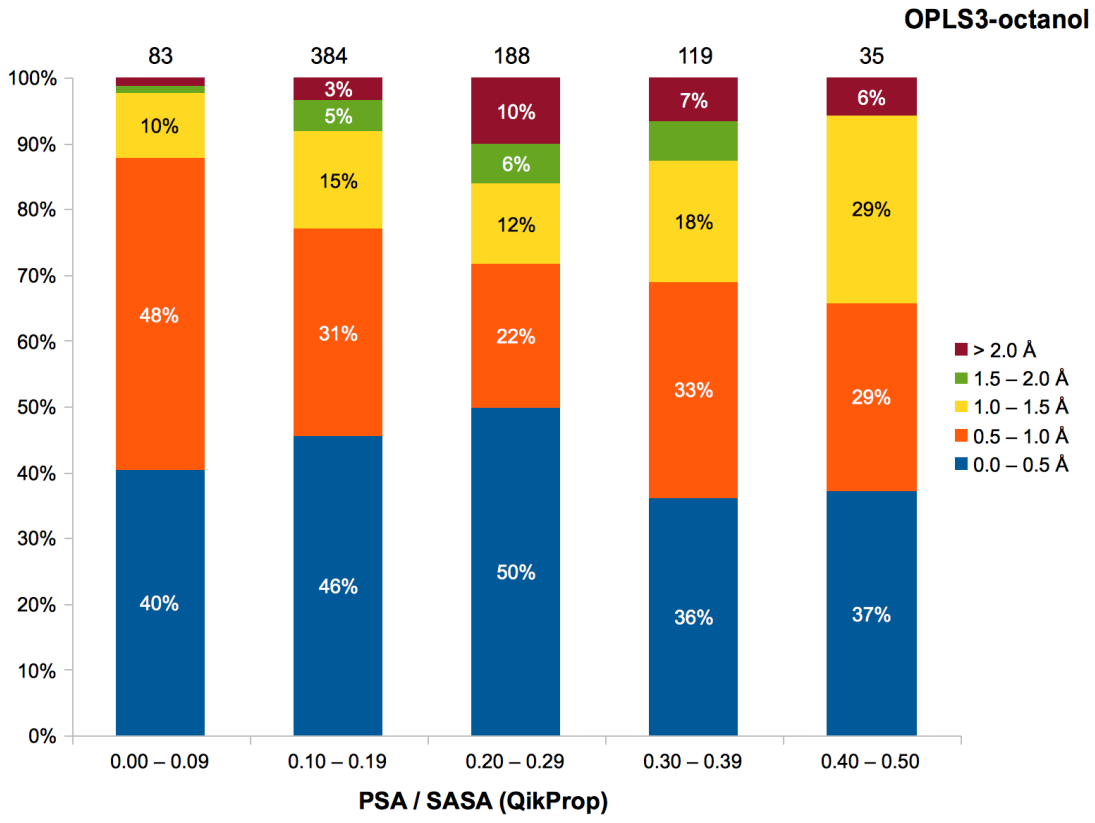

Figure S8

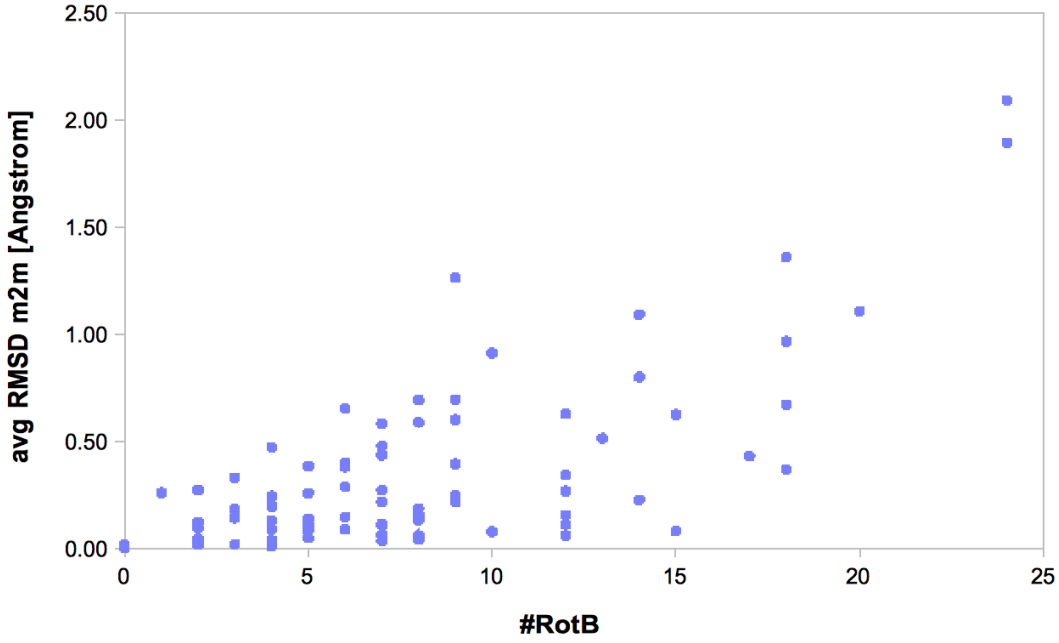

Figure S9

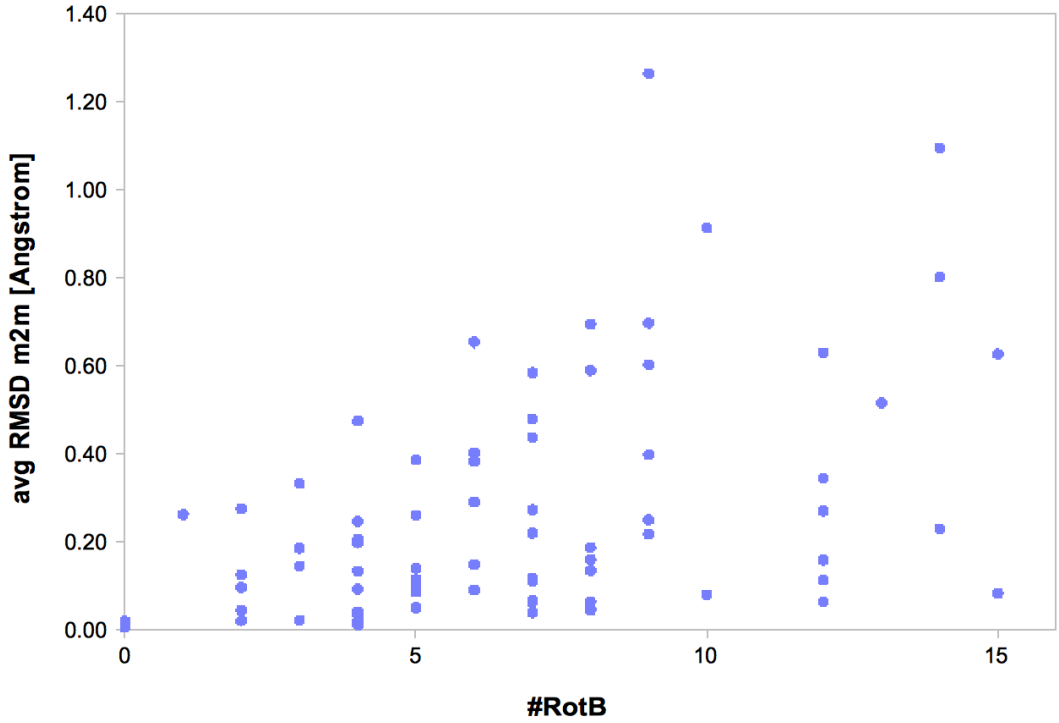

Figure S10

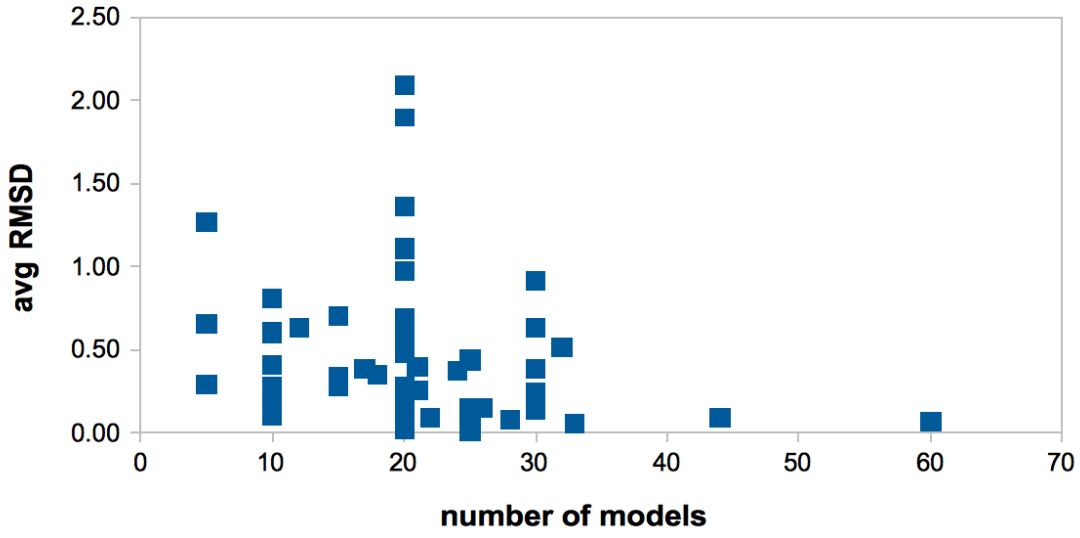

Figure S11

Figures S12 – S48 correspond to "Charged group analyses" section in the main text and show best-achieved RMSDs (most similar conformer to the crystal-pose) for ligands grouped by number of rotatable bonds (force field – solvent combination indicated at the top right corner of each figure).

Figures 12 – 24: The input structures for the conformational search were CHARGED.

Figures 25 – 36: The input structures for the conformational search were NEUTRALIZED.

Figures 37 – 48: Outcome of the conformational searches with CHARGED and NEUTRALIZED inputs was combined and best RMSD was selected for each input structure.

Abbreviations used for solvents in the figures: clf – chloroform, oct – Octanol, wat – Water

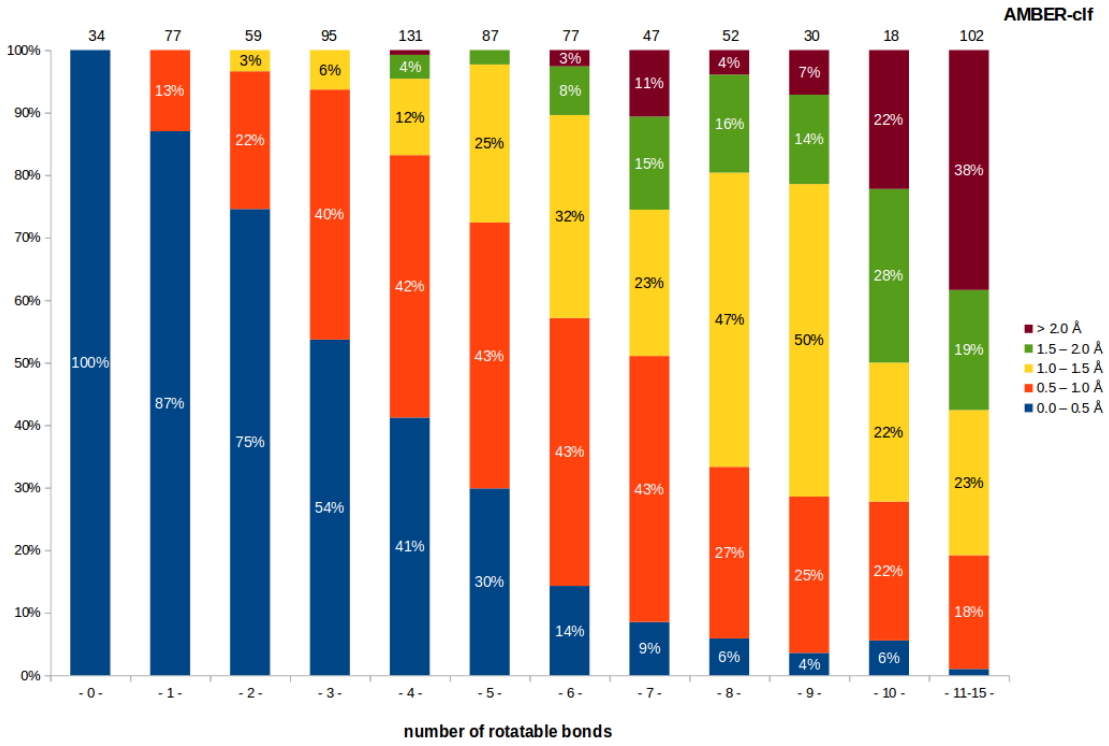

Figure S12

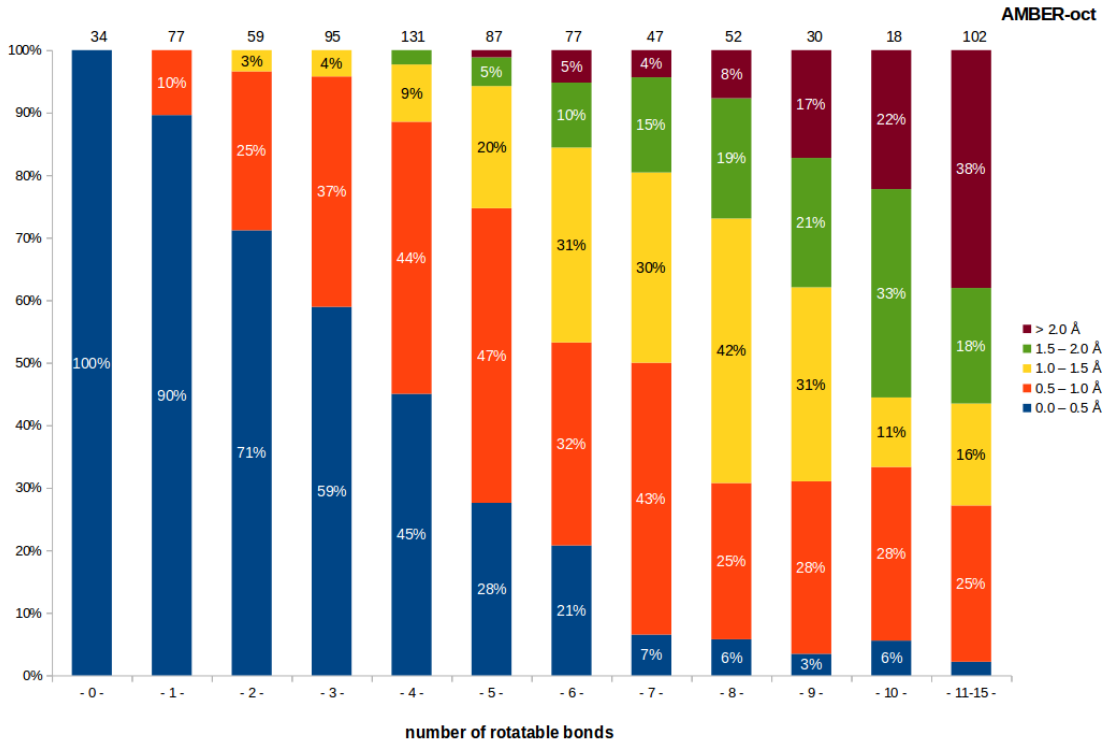

Figure S13

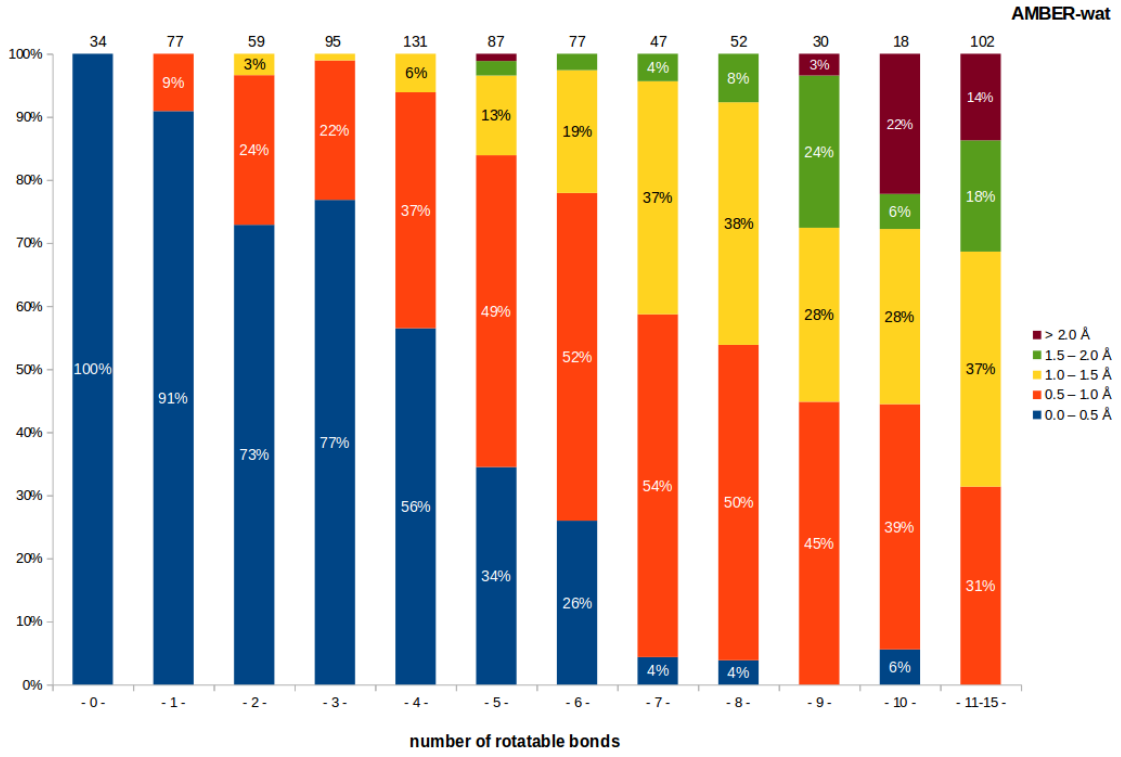

Figure S14

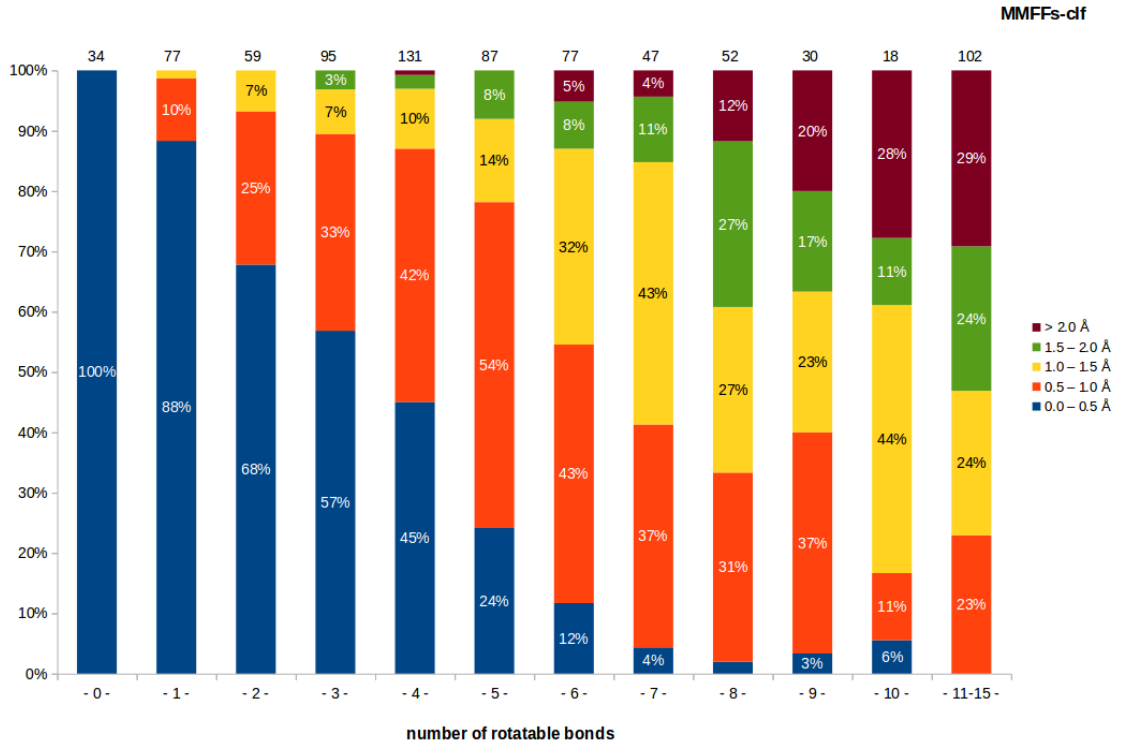

Figure S15

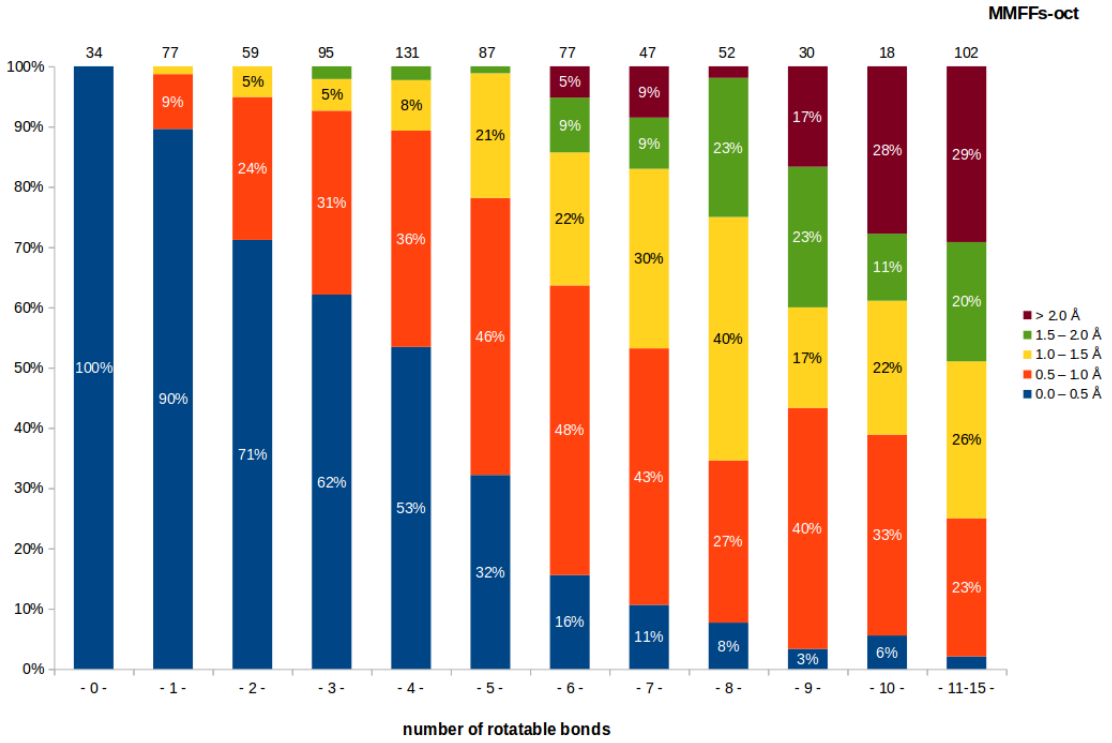

Figure S16

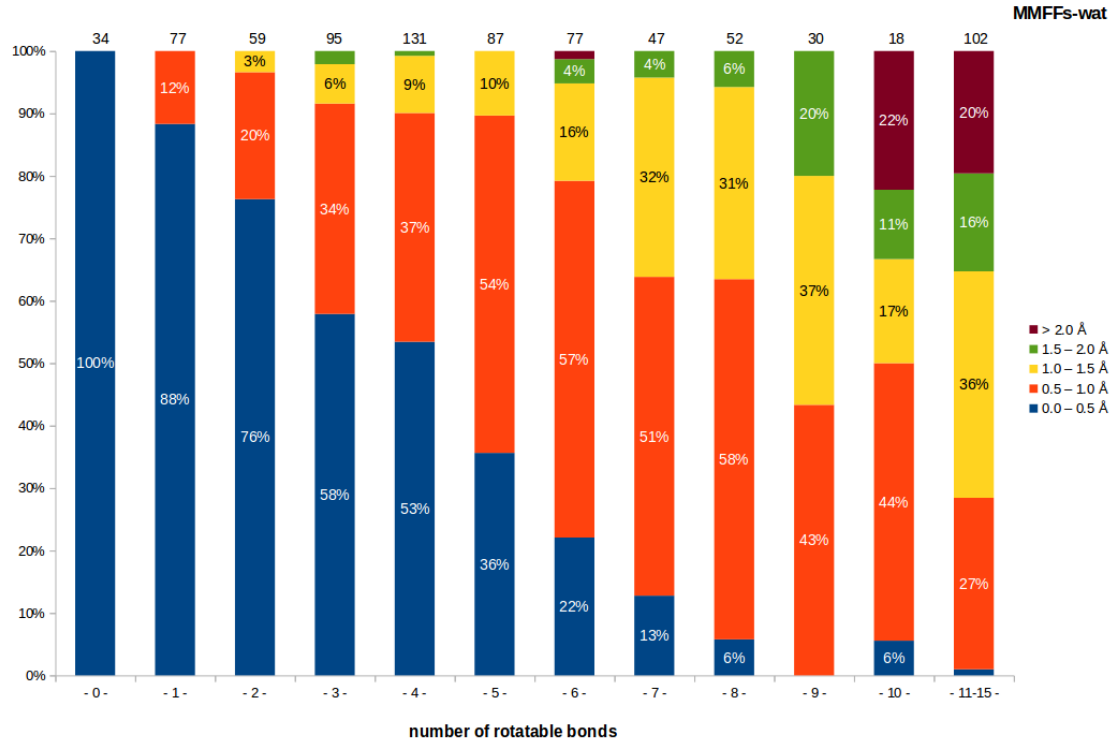

Figure S17

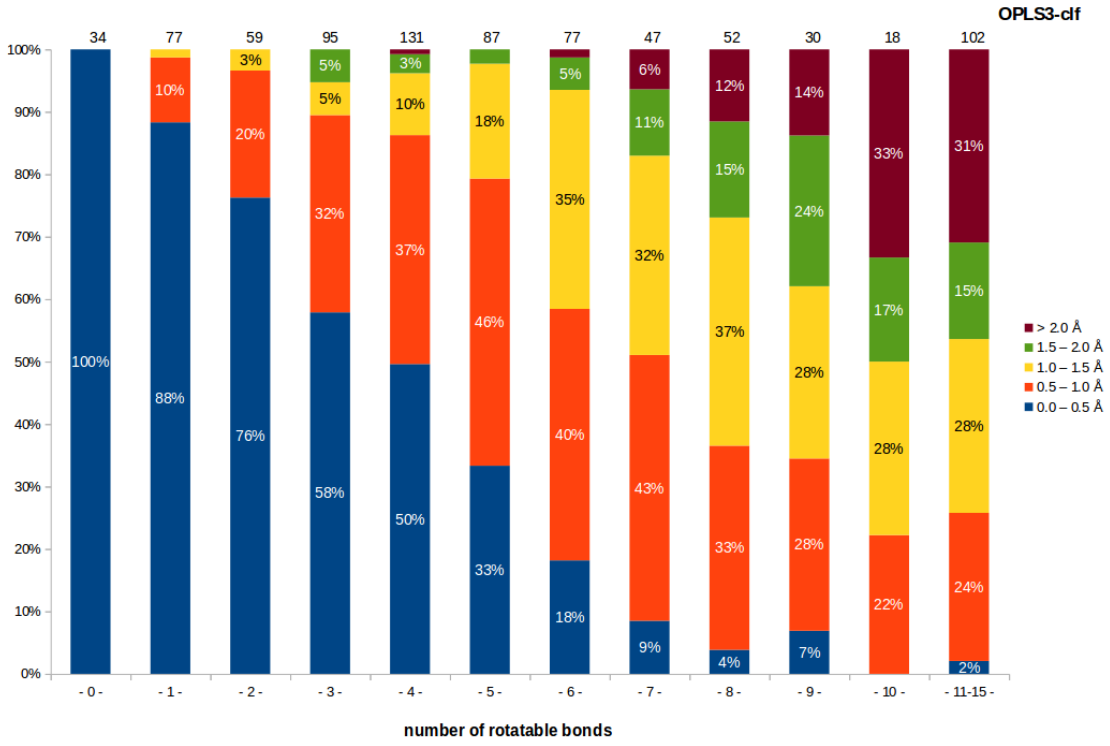

Figure S18

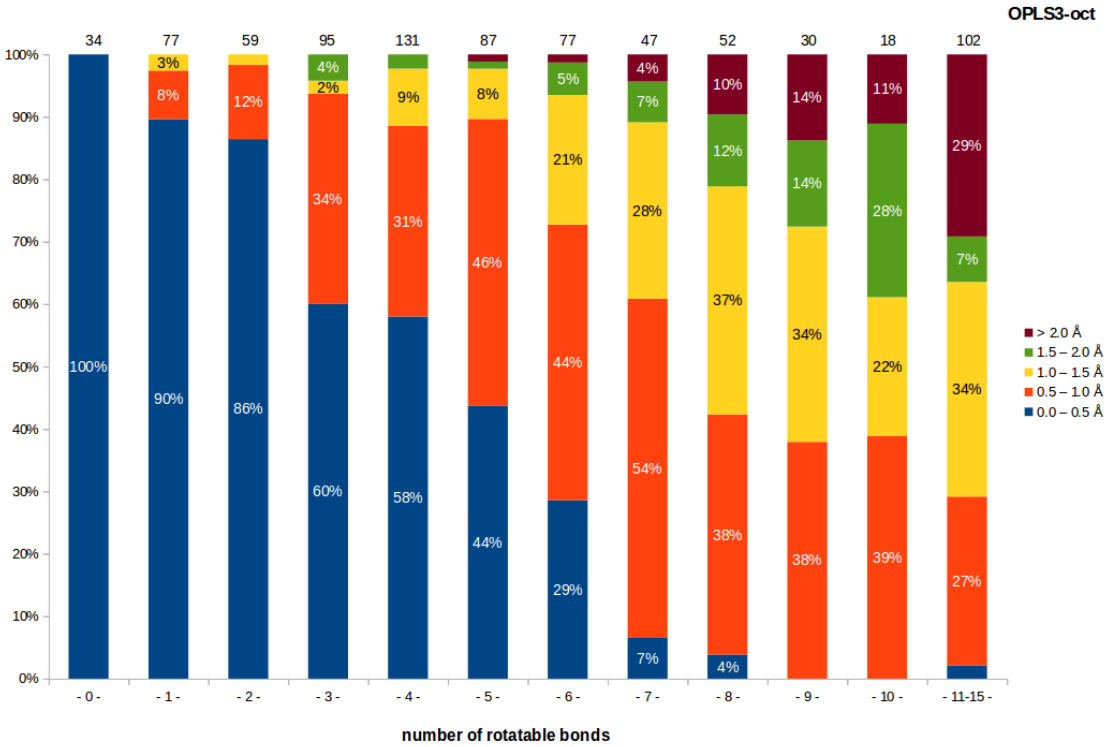

Figure S19

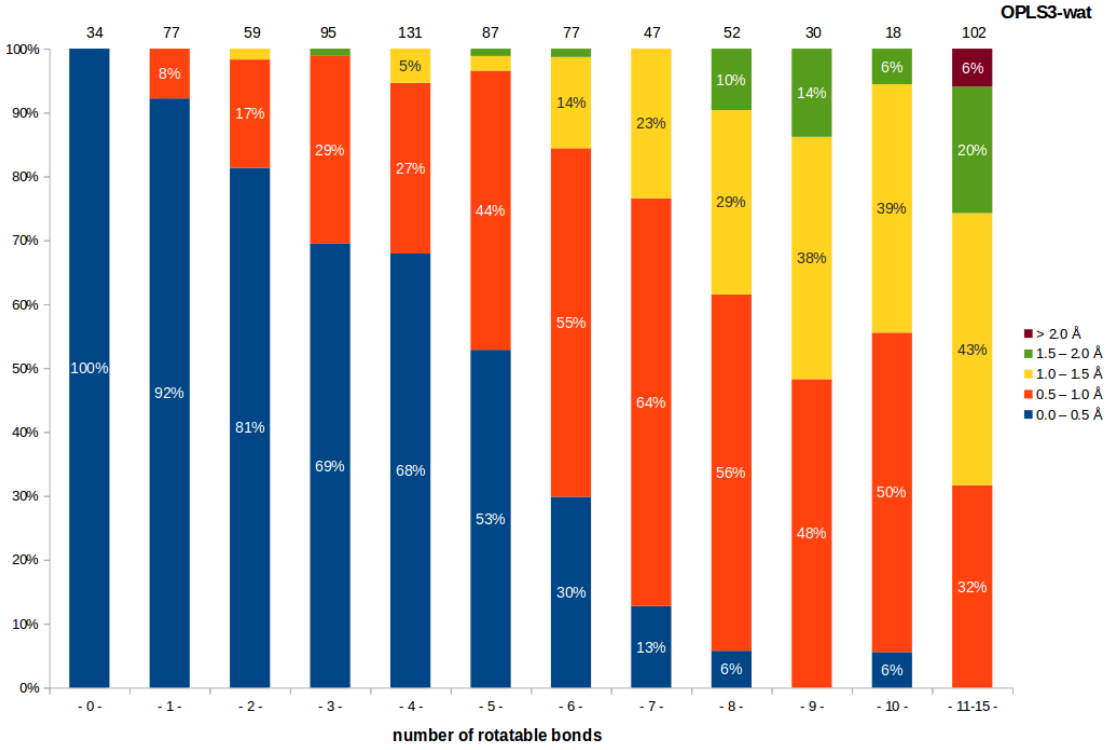

Figure S20

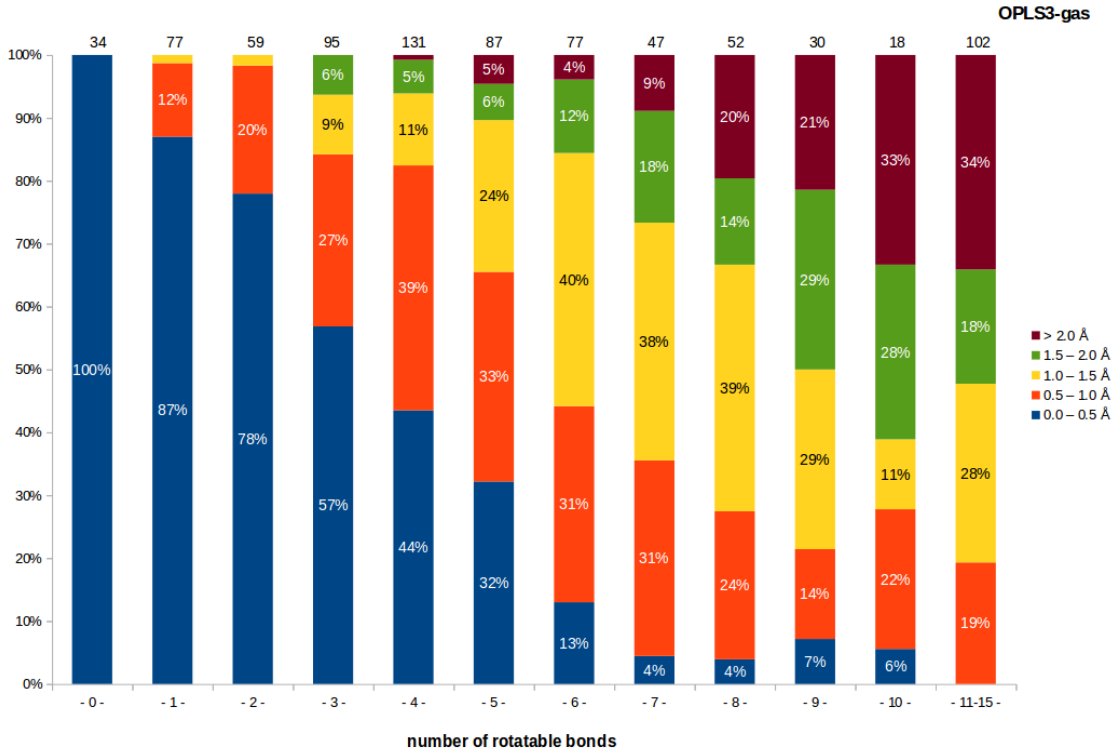

Figure S21

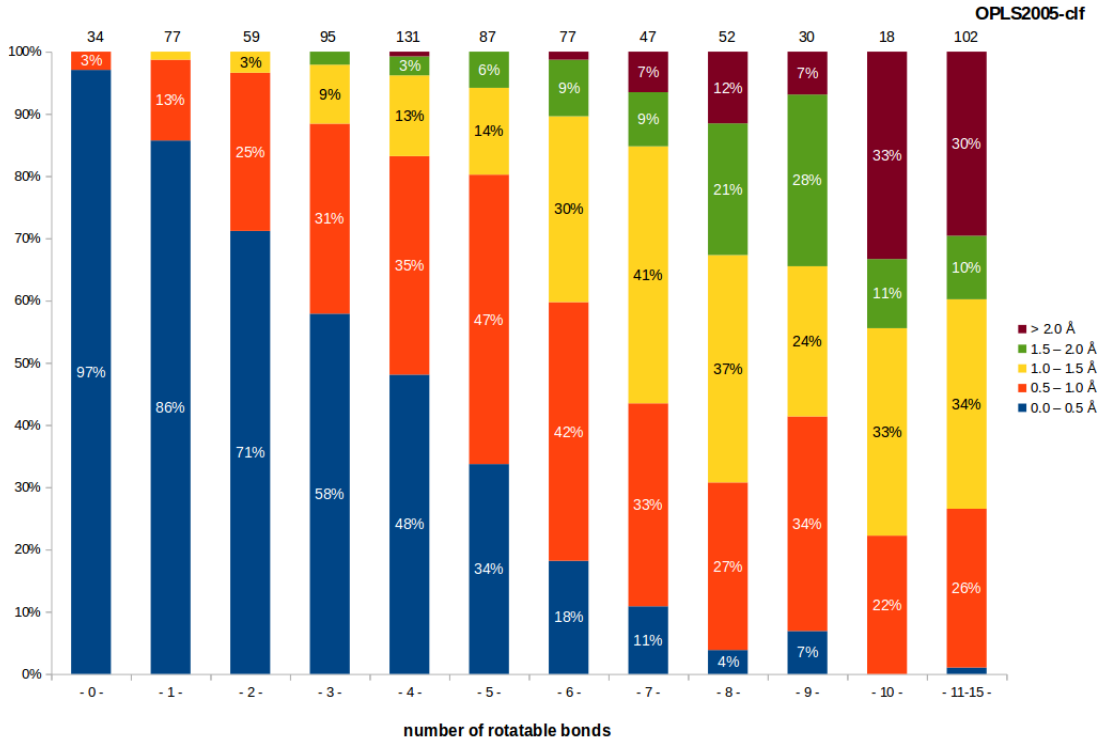

Figure S22

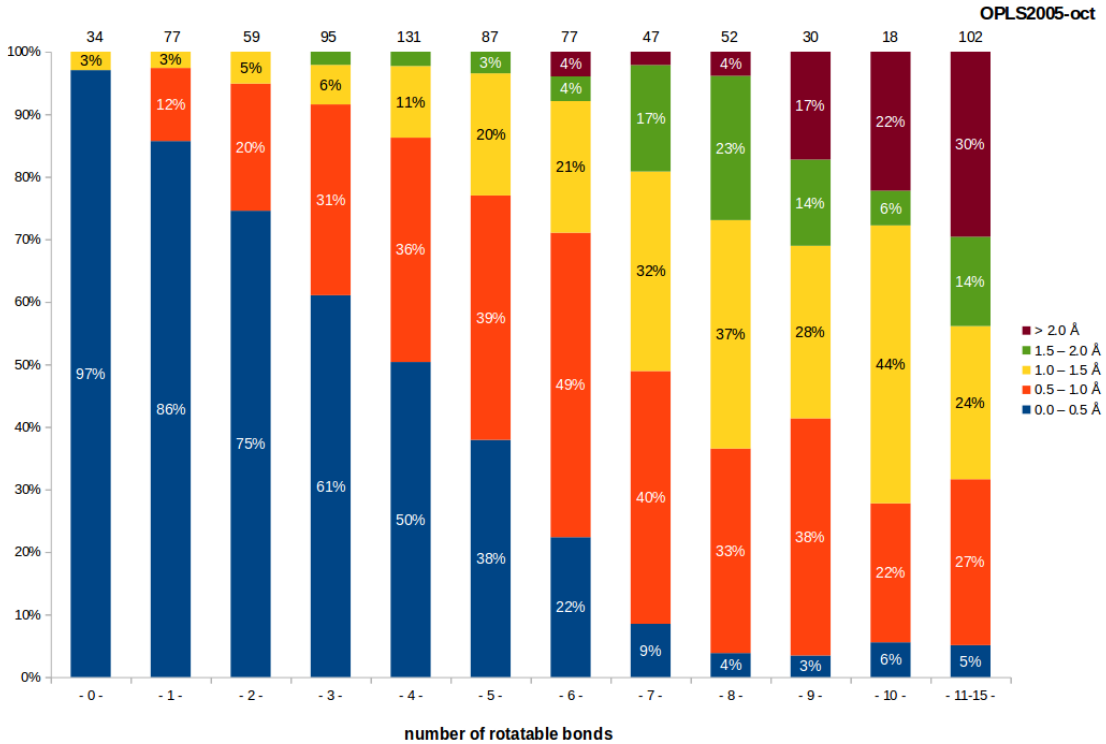

Figure S23

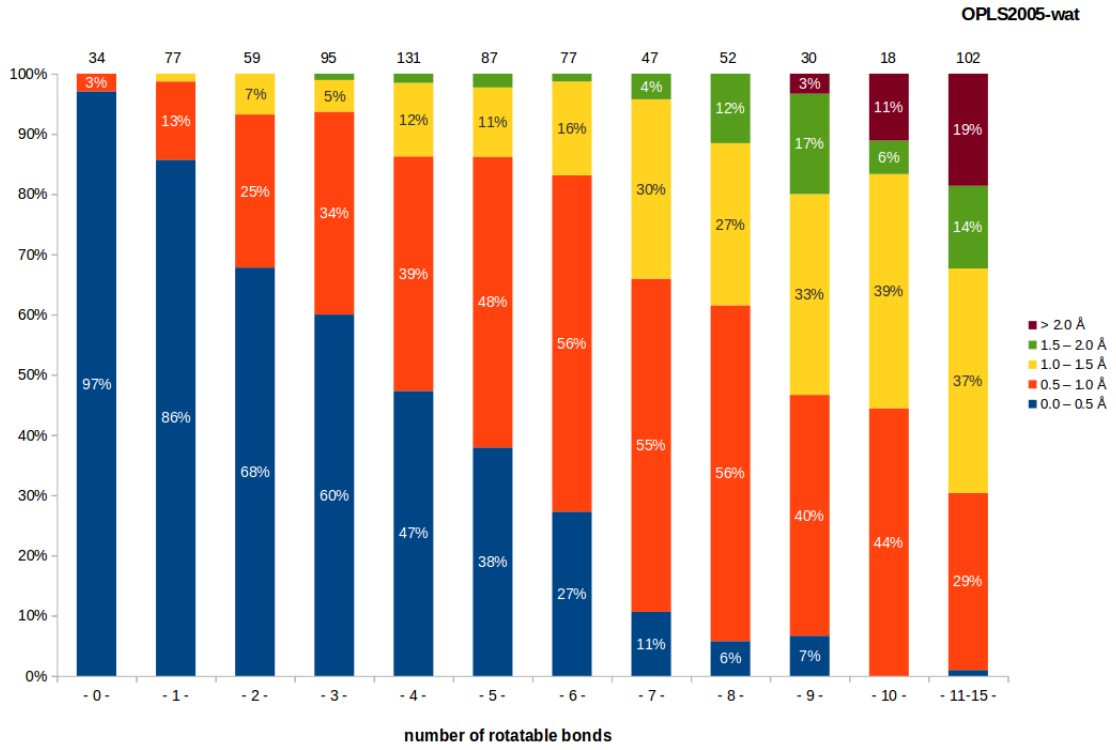

Figure S24

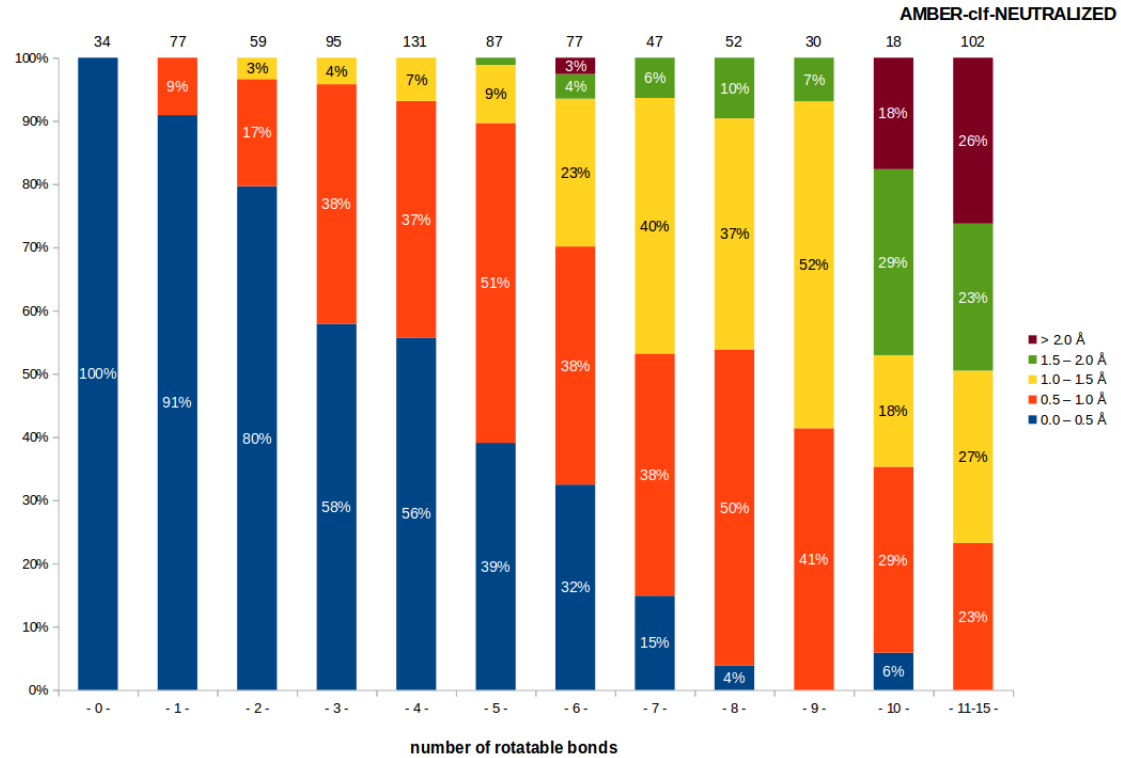

Figure S25

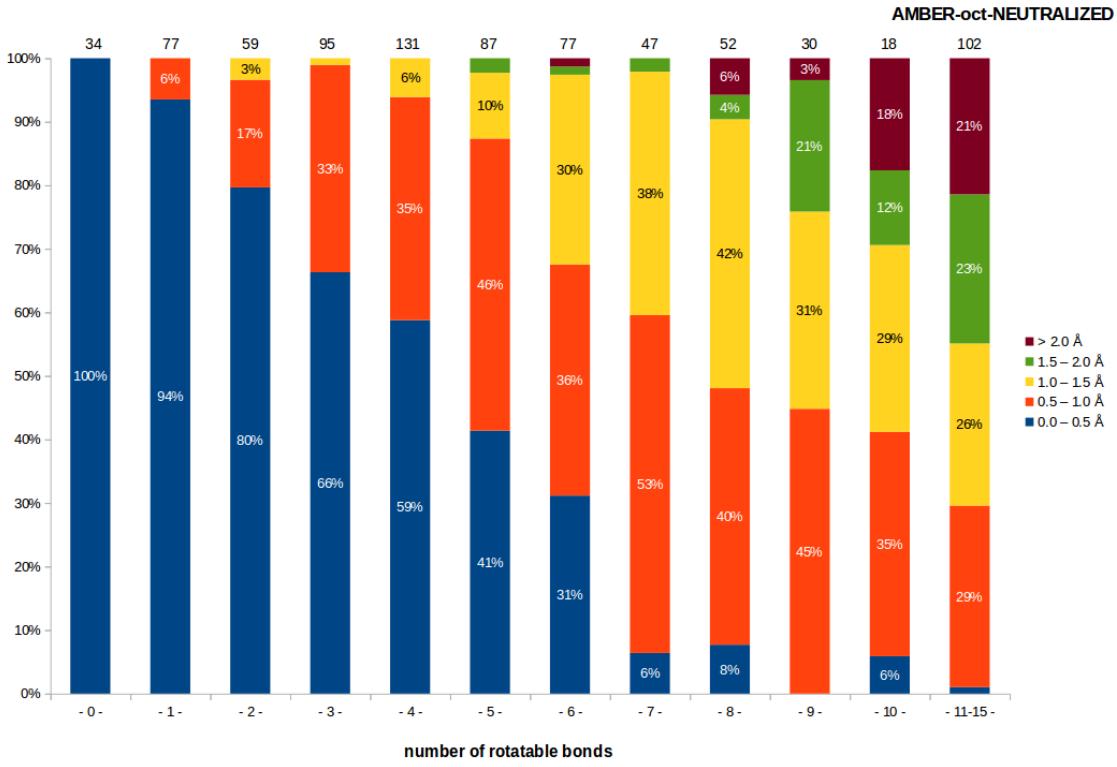

Figure S26

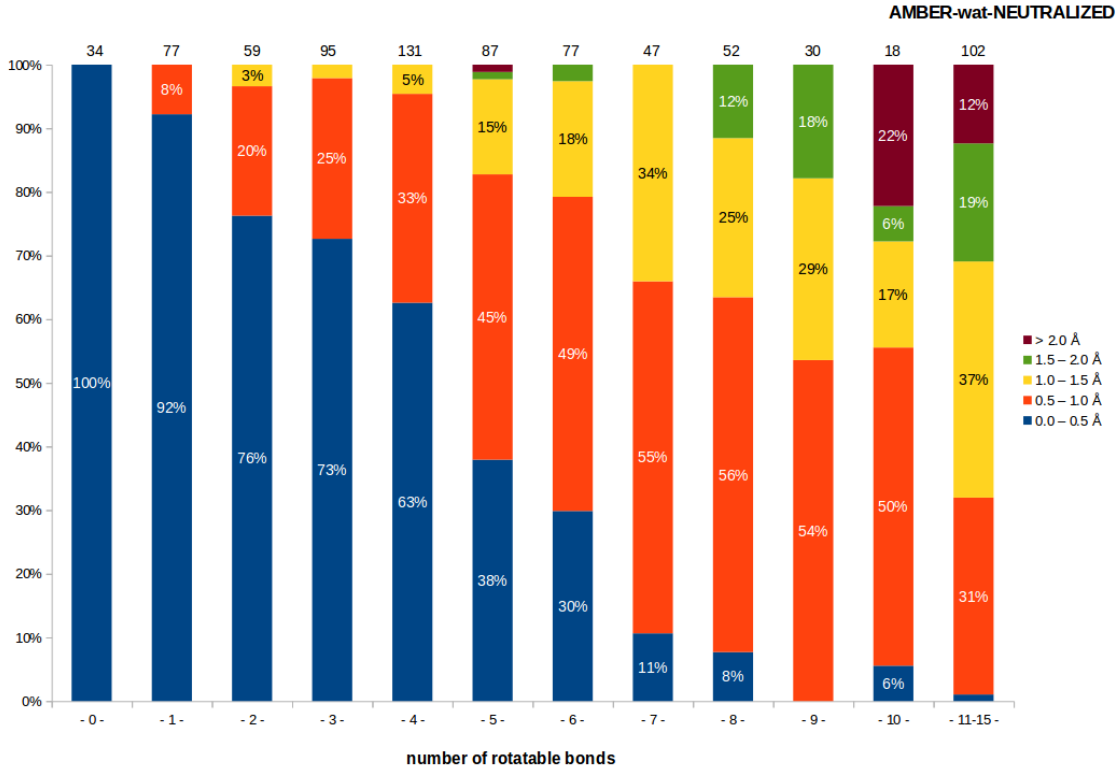

Figure S27

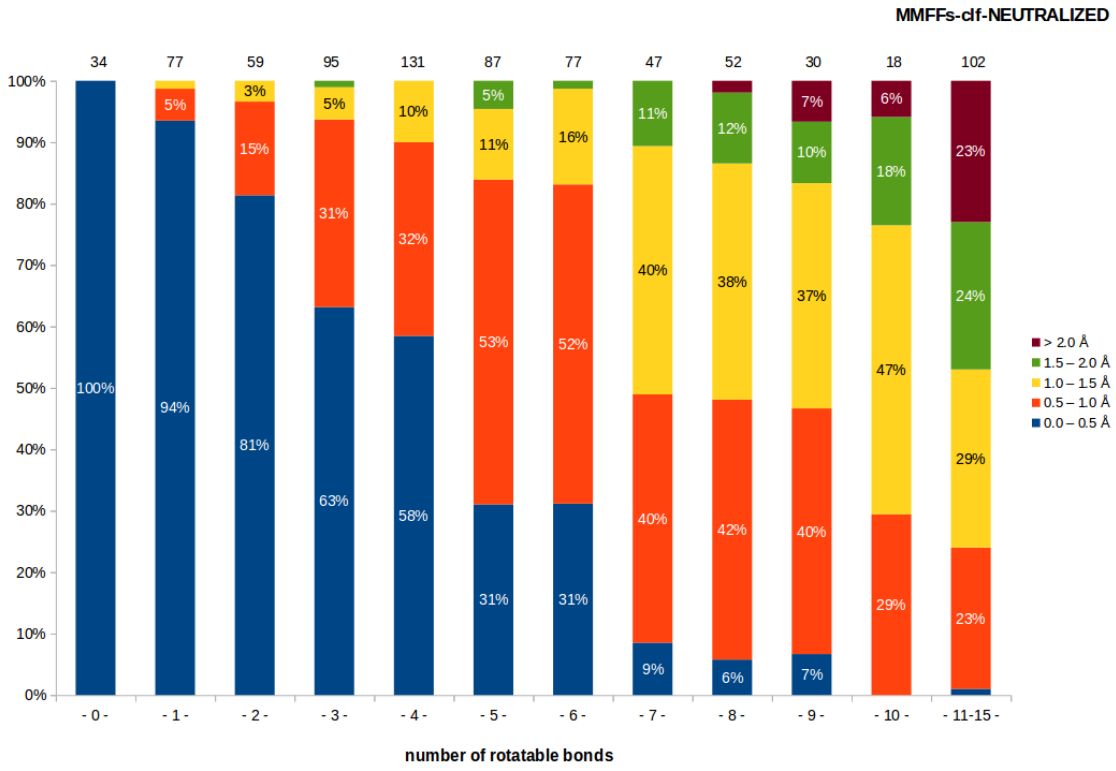

Figure S28

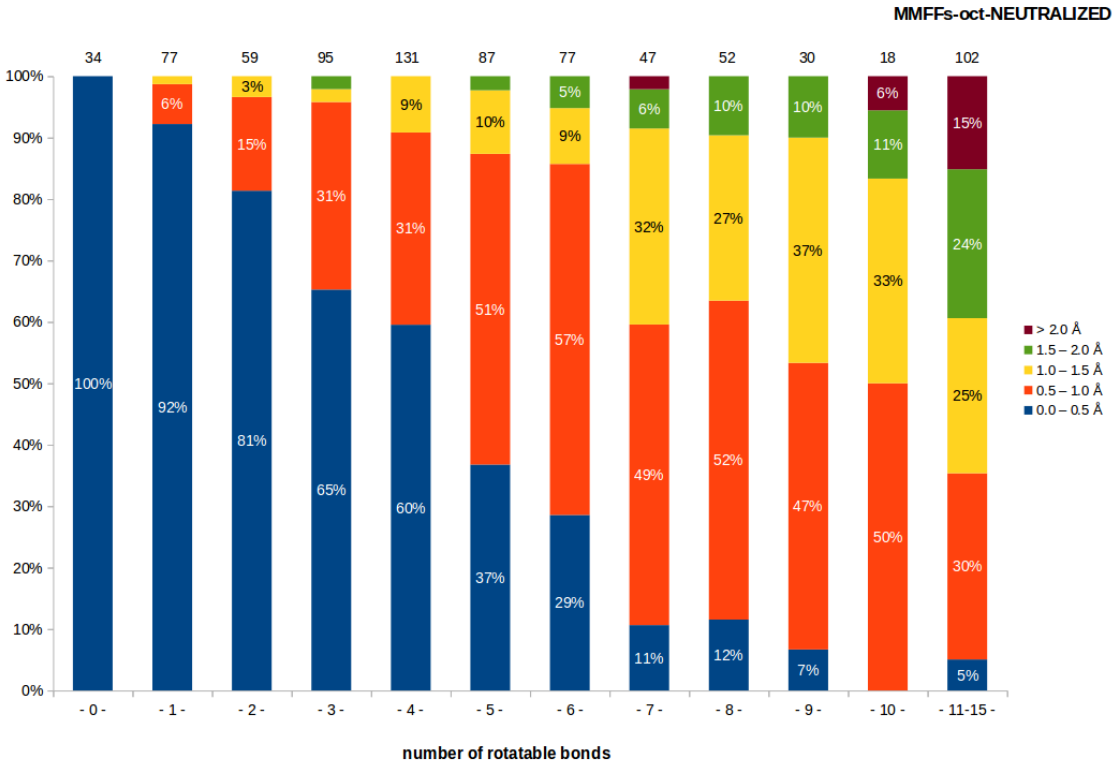

Figure S29

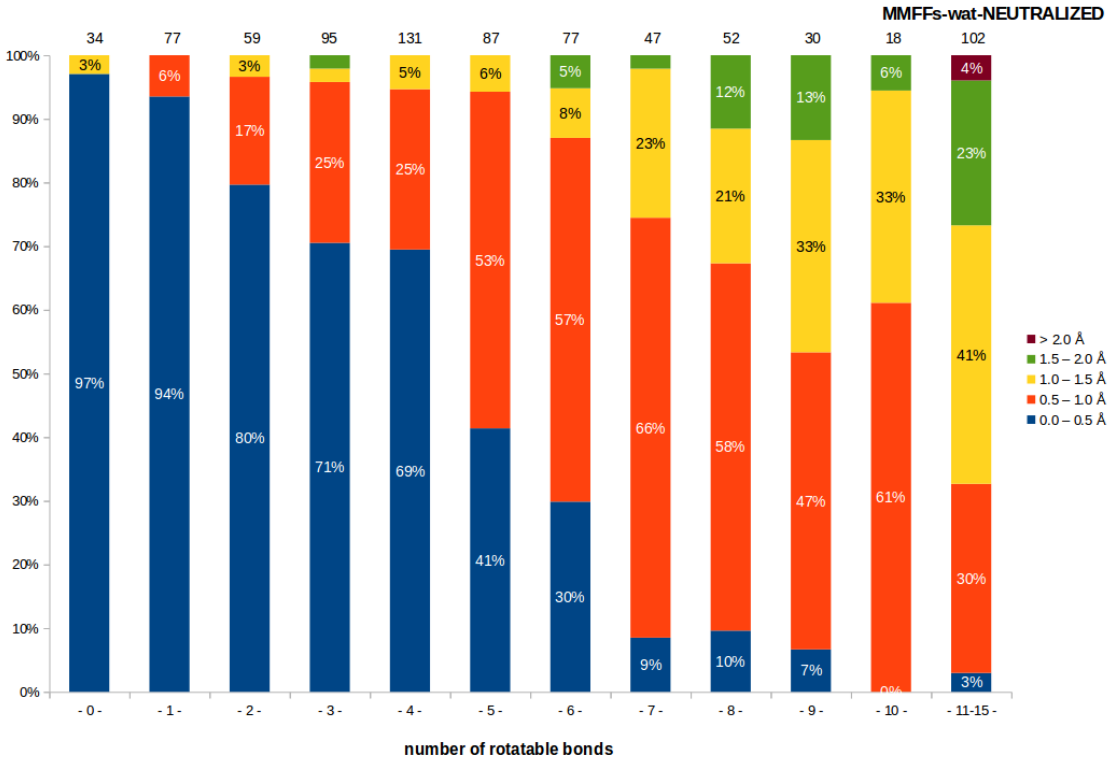

Figure S30

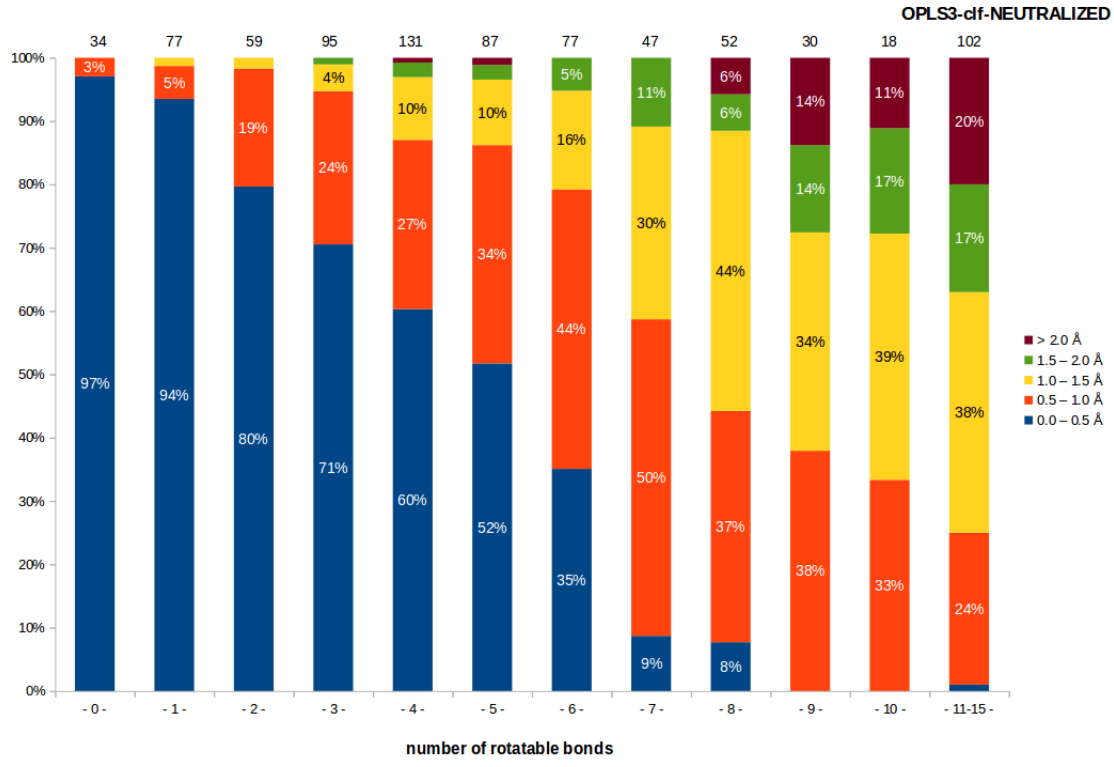

Figure S31

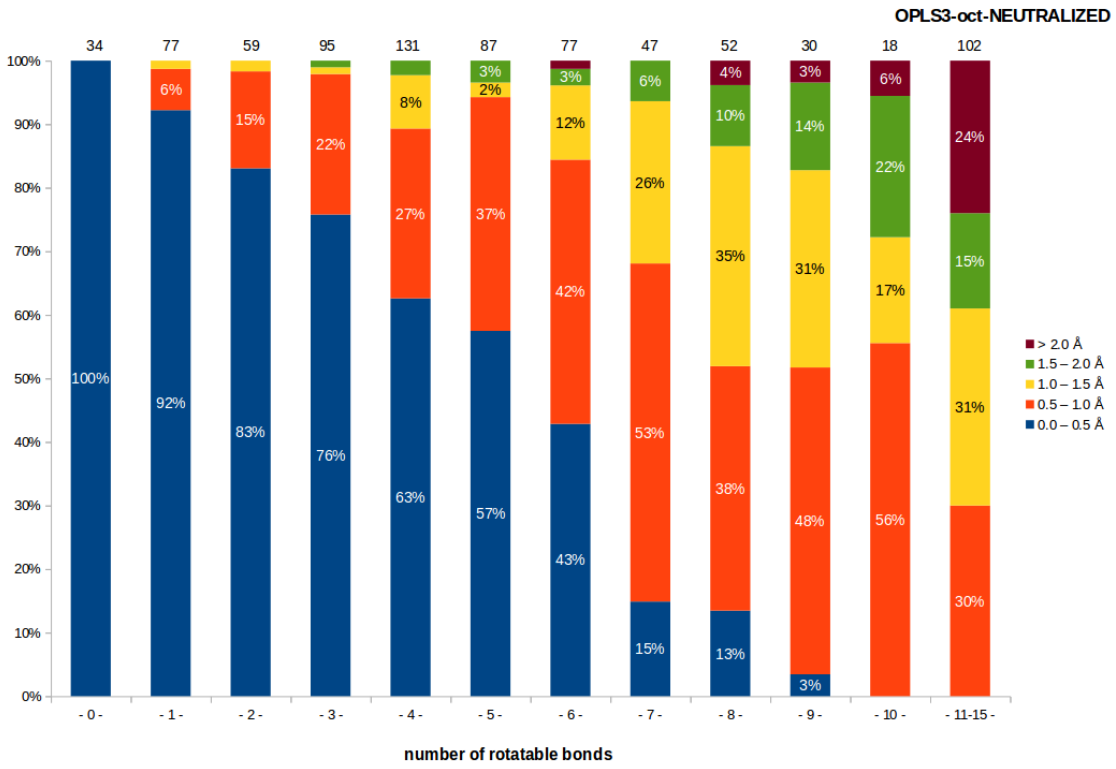

Figure S32

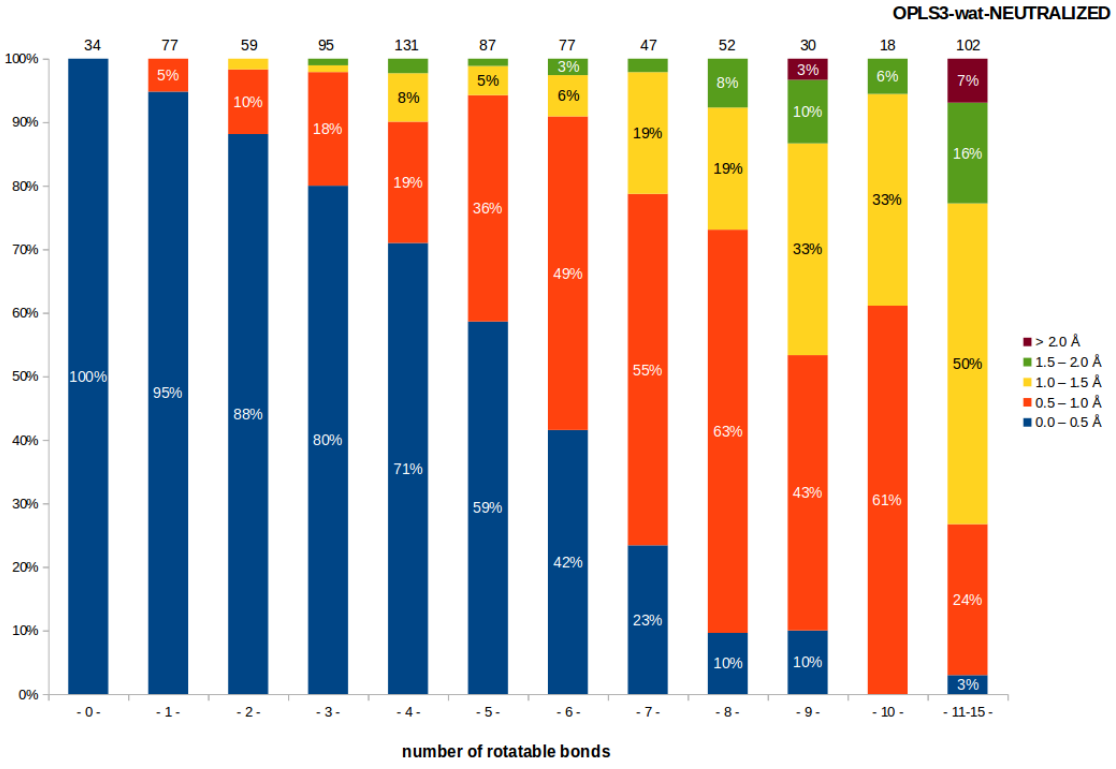

Figure S33

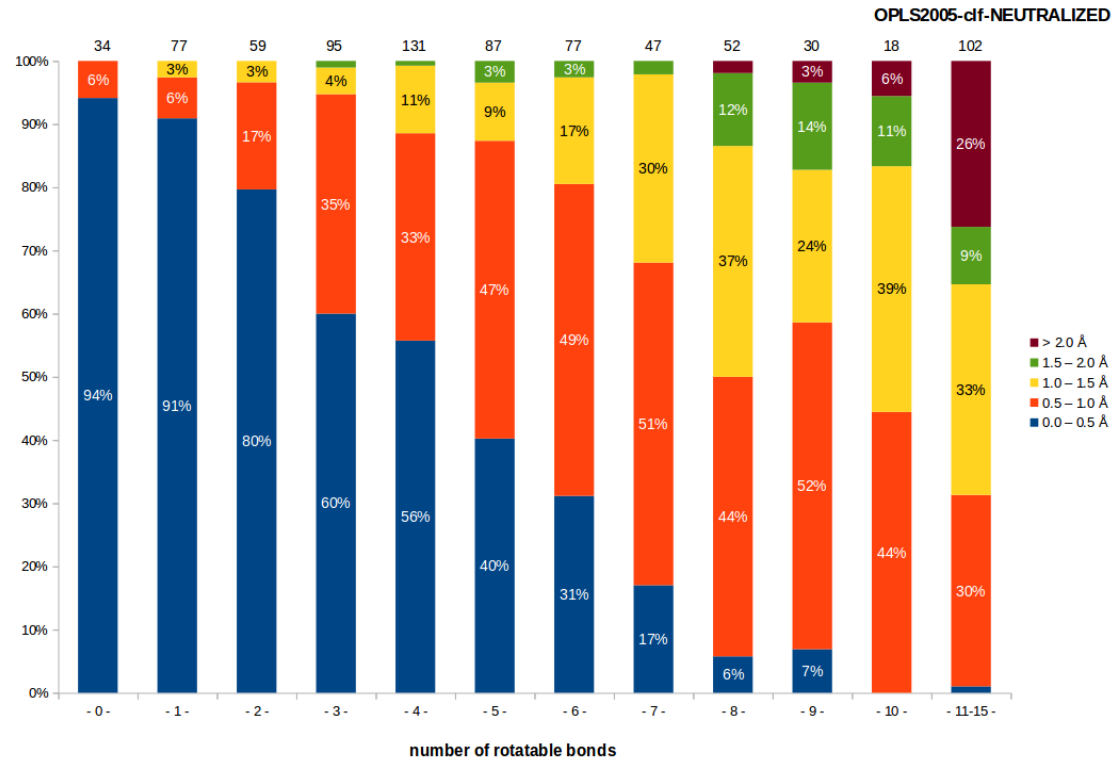

Figure S34

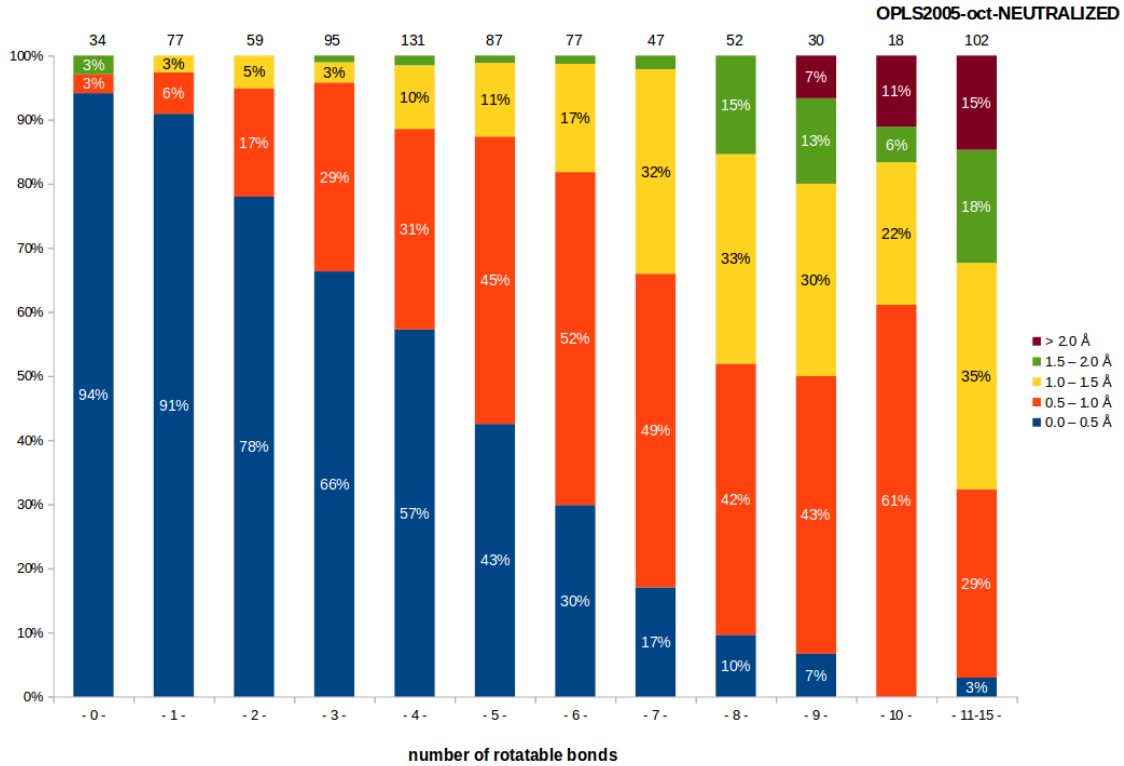

Figure S35

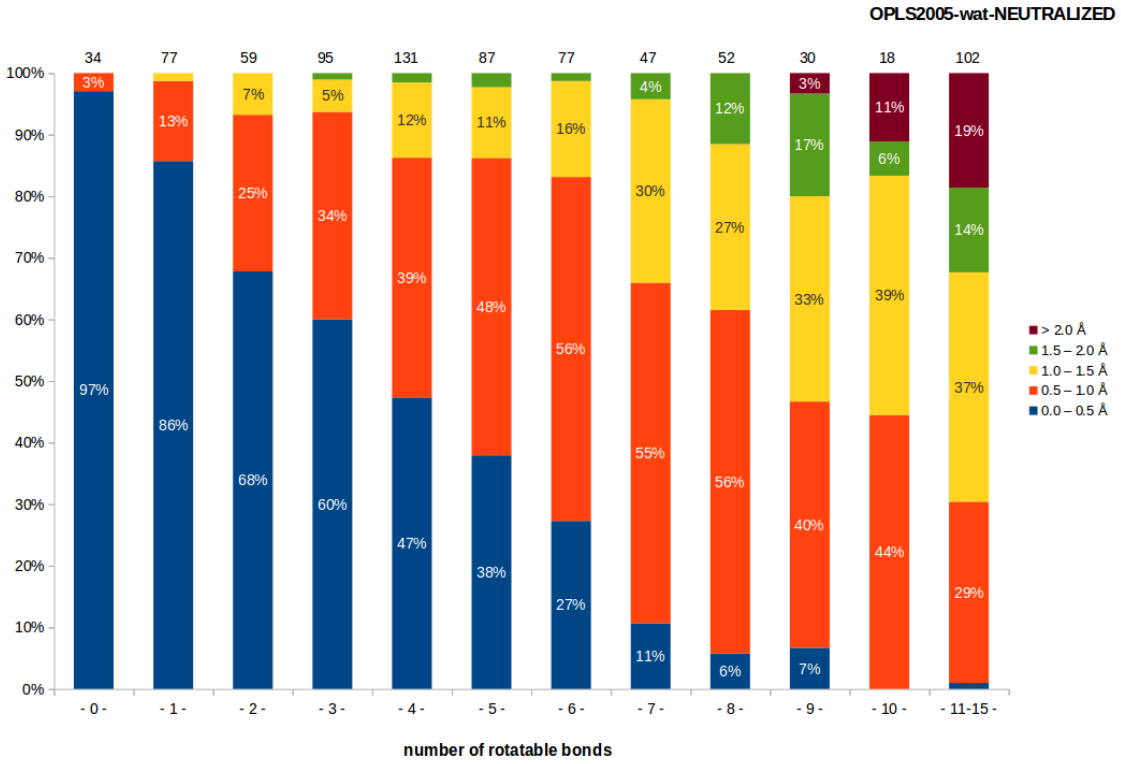

Figure S36

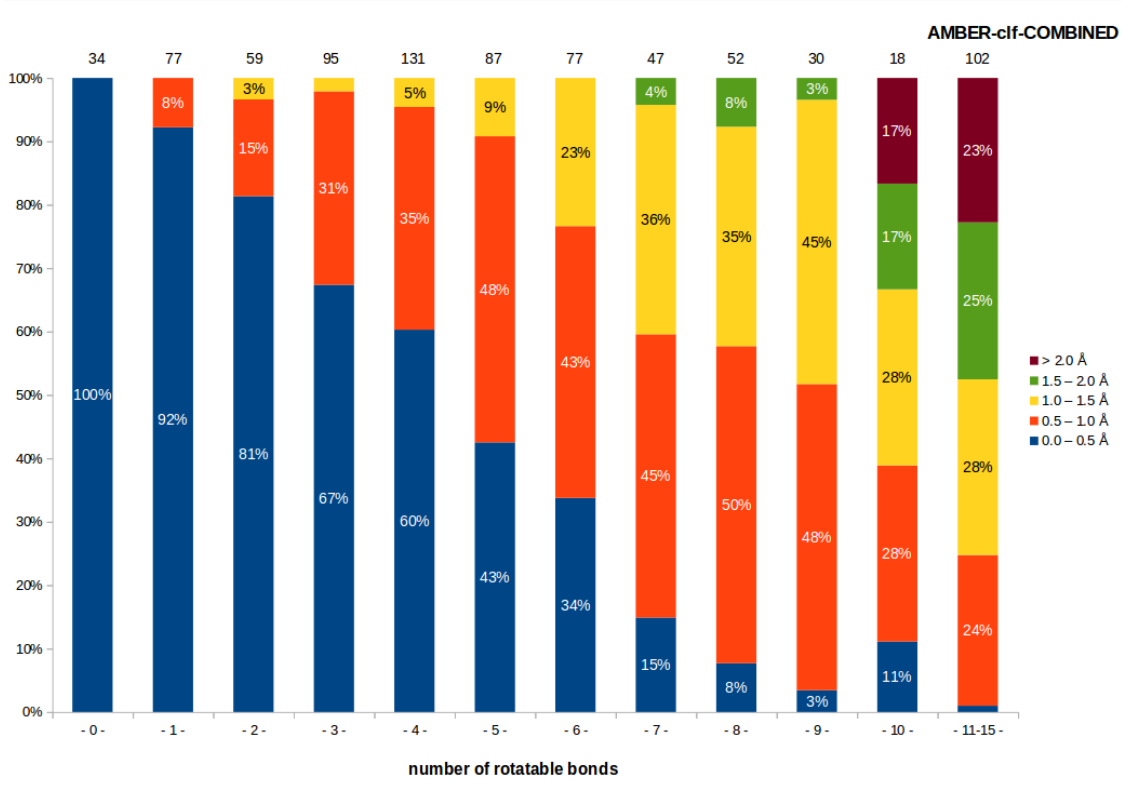

Figure S37

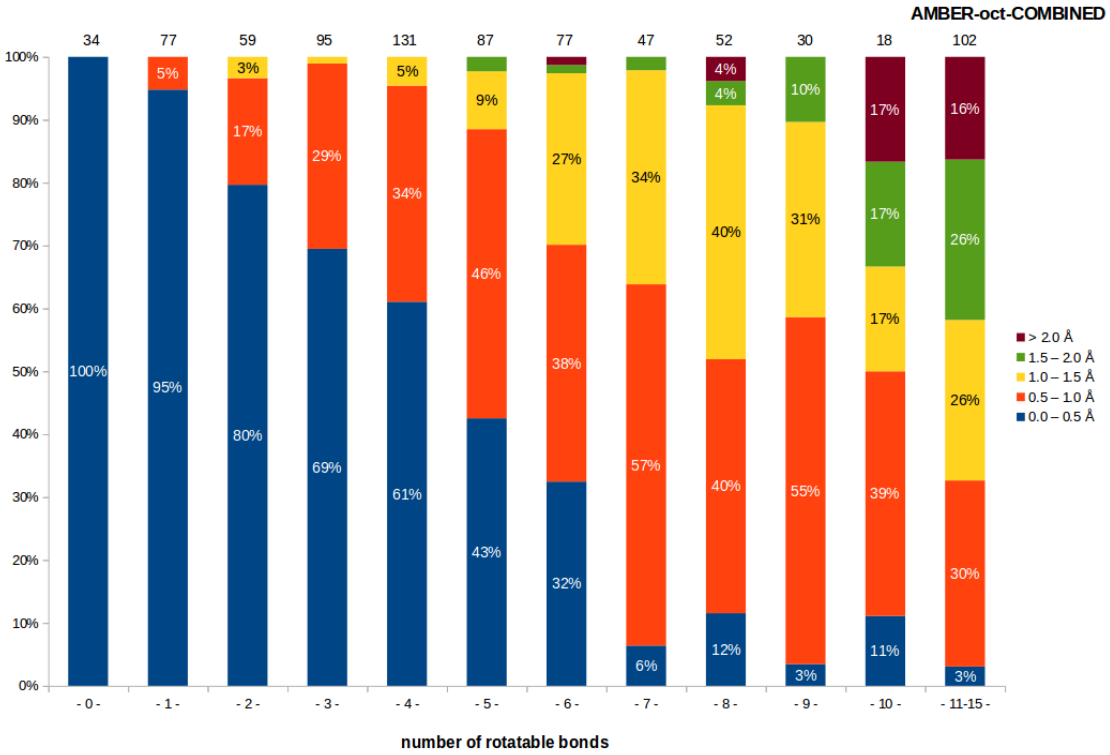

Figure S38

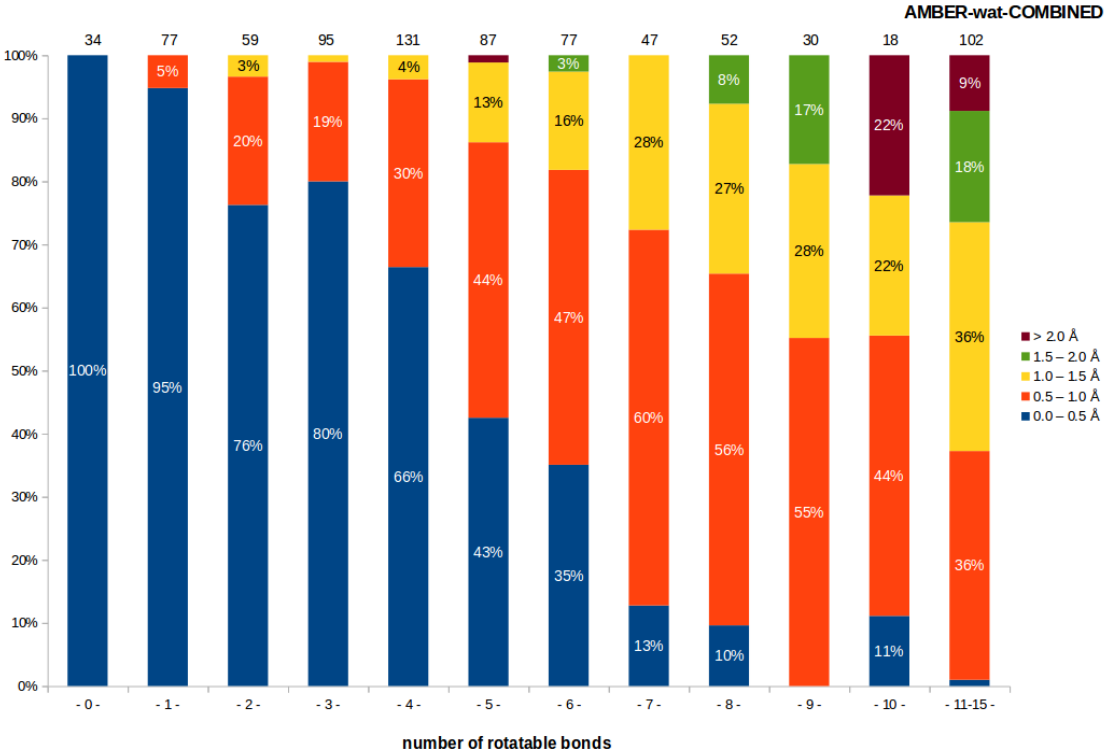

Figure S39

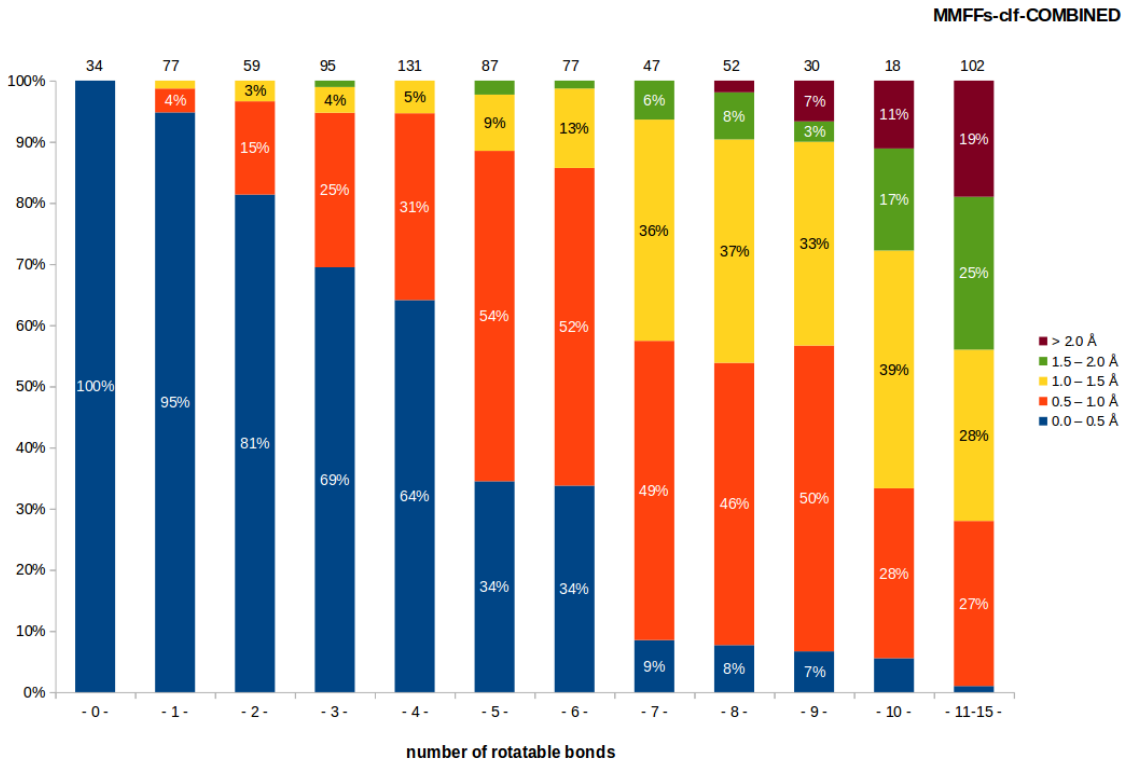

Figure S40

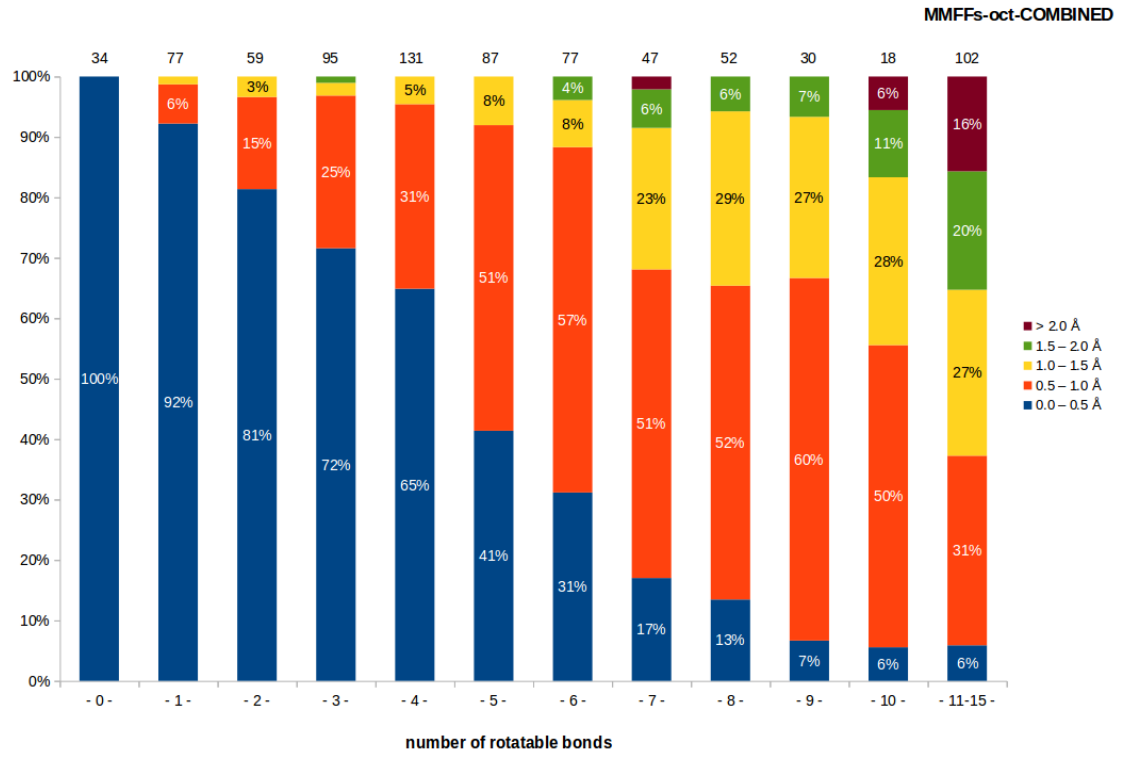

Figure S41

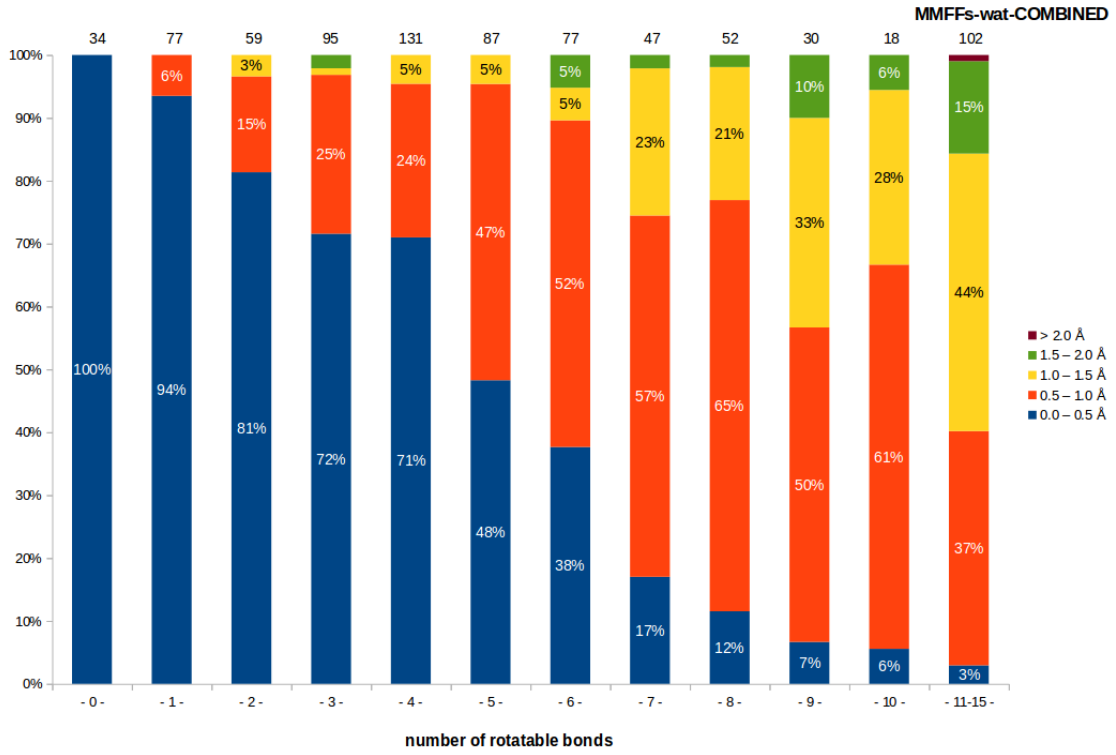

Figure S42

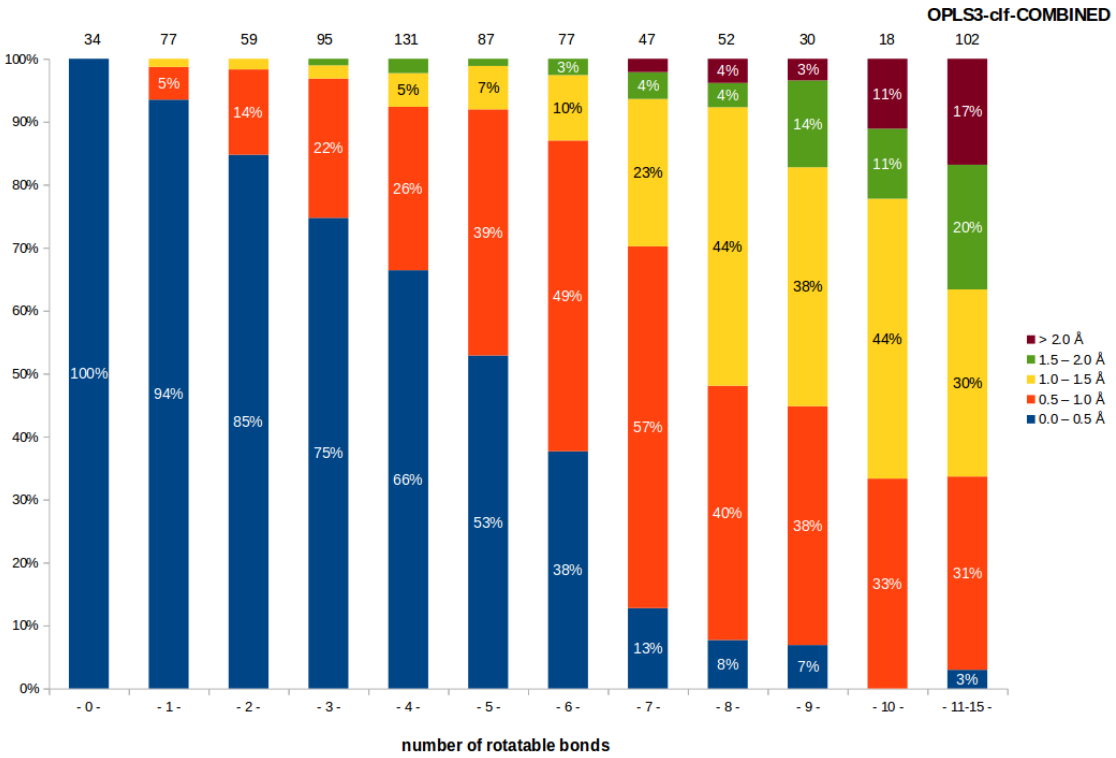

Figure S43

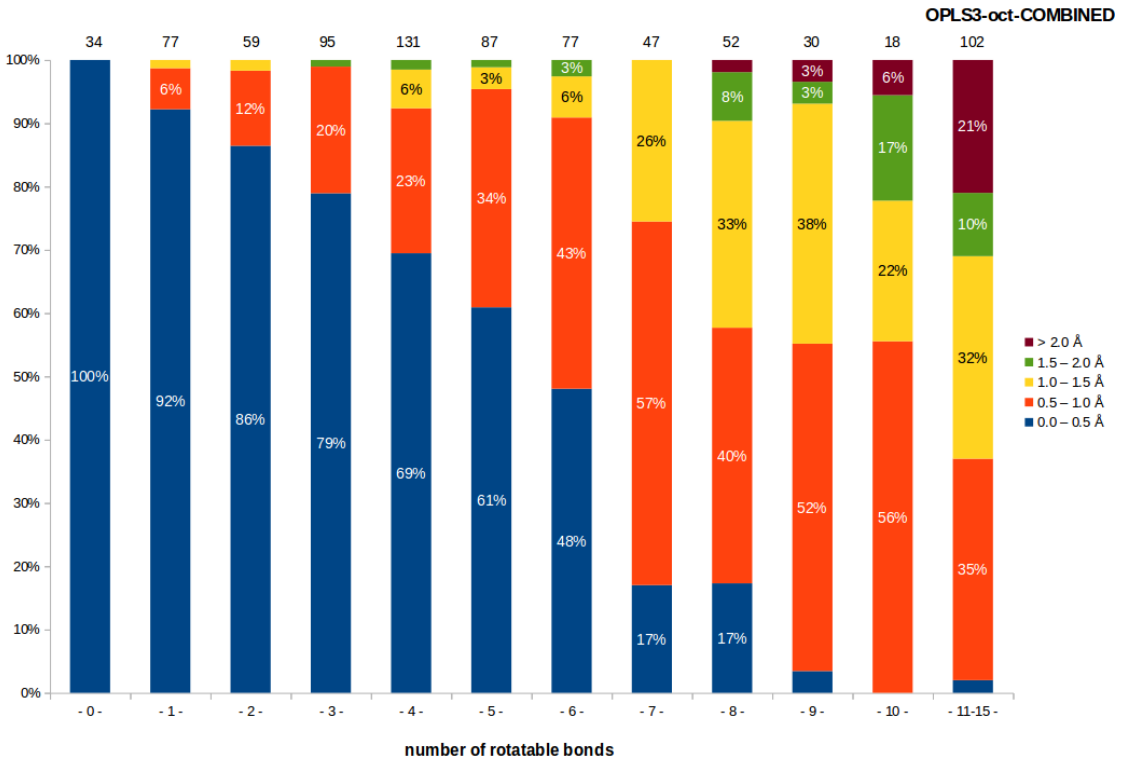

Figure S44

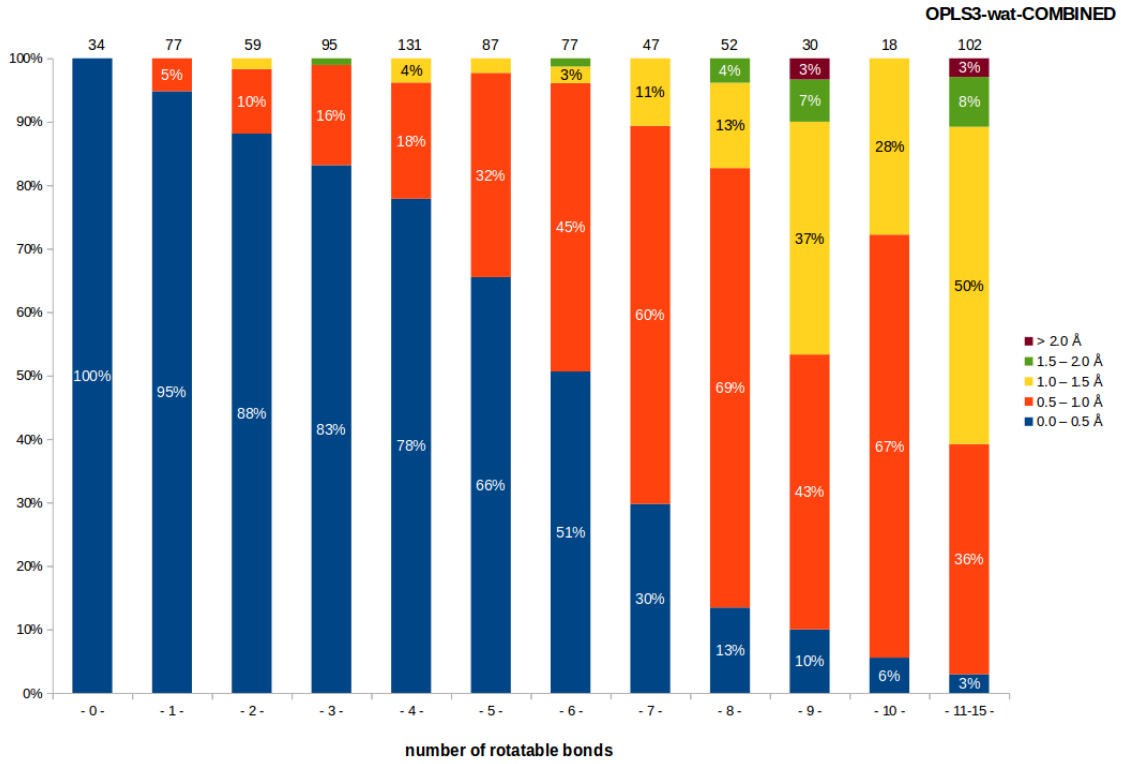

Figure S45

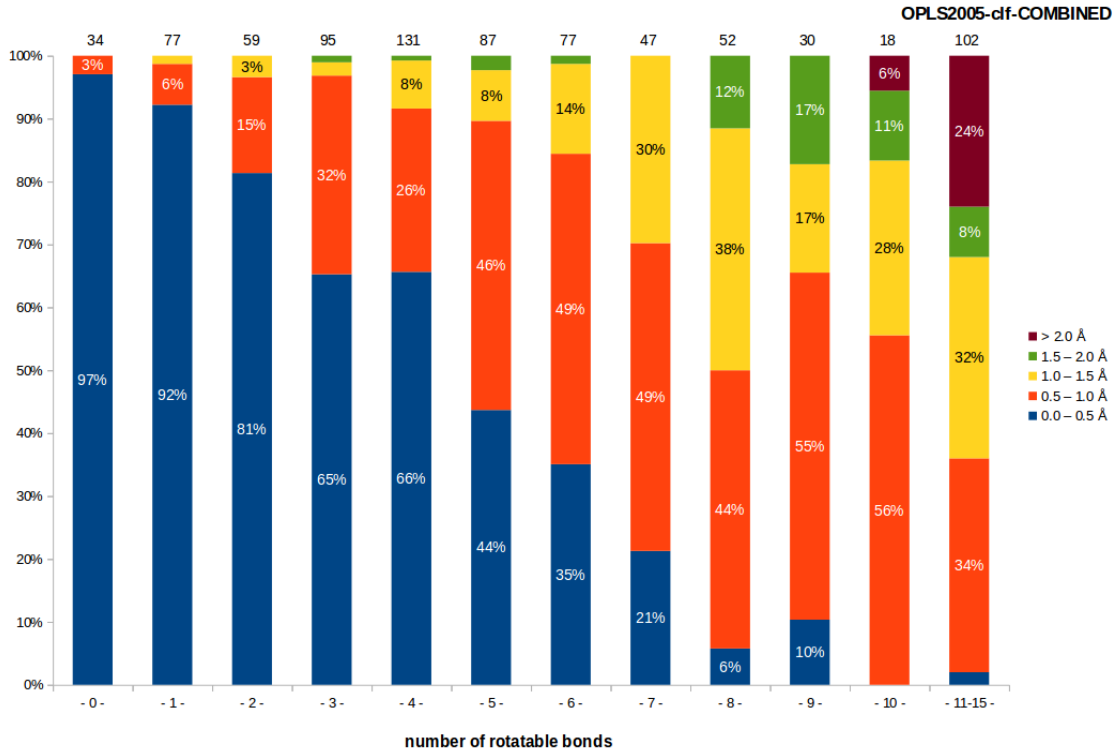

Figure S46

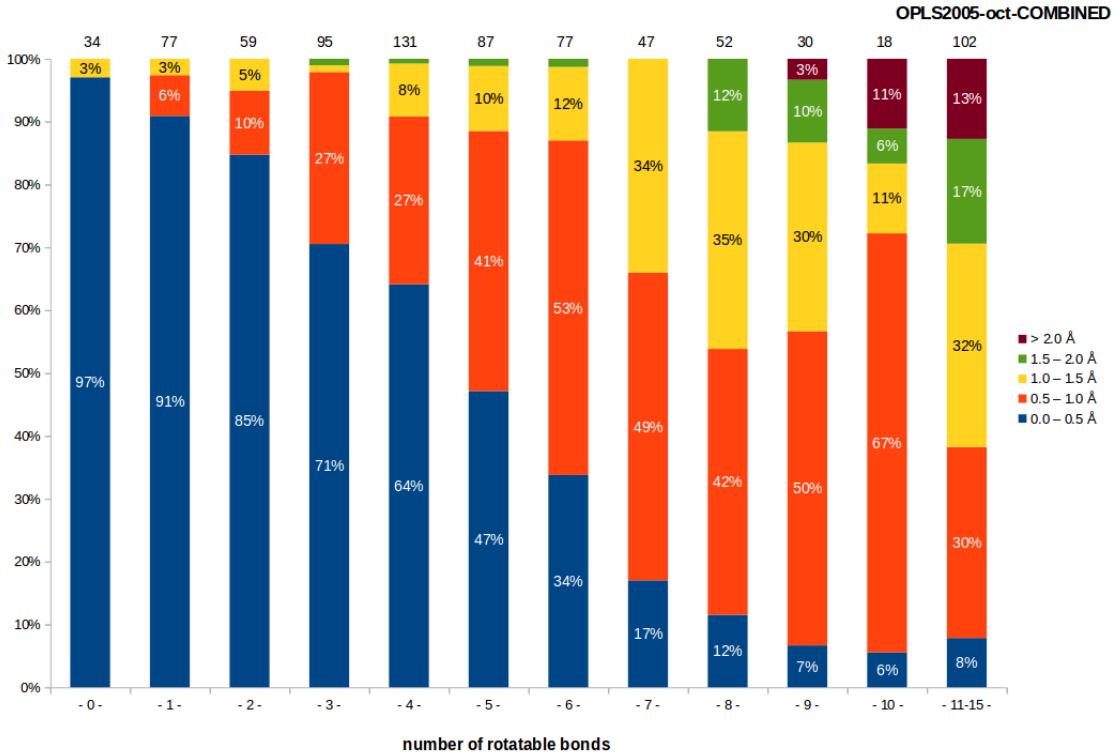

Figure S47

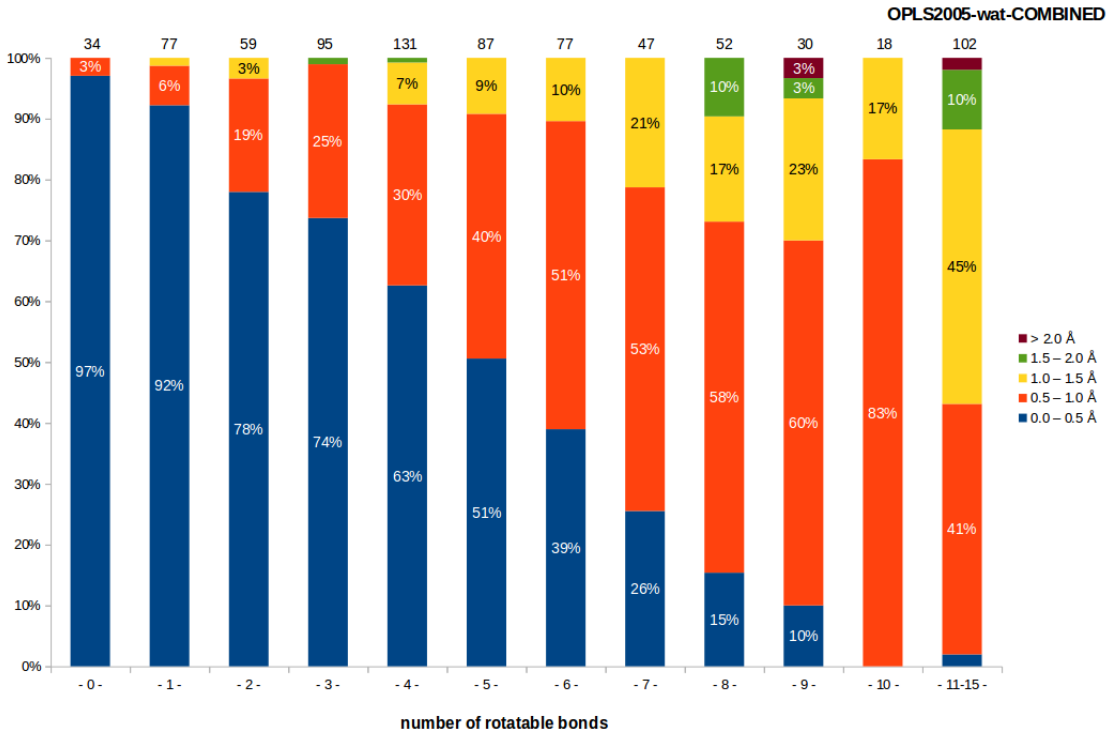
OPLS2005-wat-COMBINED
34
77
59
95
131
87
77
47
52
30
18
102
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
3%
6%
3%
19%
25%
7%
30%
9%
40%
10%
51%
21%
53%
10%
17%
58%
3%
3%
23%
60%
17%
83%
10%
45%
41%
97%
92%
78%
74%
63%
51%
39%
26%
15%
10%
- 0 -
- 1 -
- 2 -
- 3 -
- 4 -
- 5 -
- 6 -
- 7 -
- 8 -
- 9 -
- 10 -
- 11-15 -
number of rotatable bonds
> 2.0 Å
1.5 – 2.0 Å
1.0 – 1.5 Å
0.5 – 1.0 Å
0.0 – 0.5 Å

Figure S48