# Catalytic Mechanism of Aromatic Prenylation by NphB

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## S1. Abbreviations

| | |
|---|---|
| SCC-DFTB: | self-consistent-charge density-functional tight-binding; |
| QM: | quantum mechanics; |
| MD: | molecular dynamics; |
| SMD: | steered molecular dynamics; |
| US: | umbrella sampling; |
| MM: | molecular mechanics; |
| PMF: | potential of mean force; |

**S1. Additional Method and Computation Details**

In recent years the SCC-DFTB/MM method has been extensively applied to enzymatic studies[1,2] with good success[3-6]. In a recent work focused on β-lactamase CphA[6], the authors reported a 1 kcal/mol difference between SCC-DFTB/MM (SCC-DFTB/CHARMM) and BLYP/MM (BLYP/AMBERff99)[7] and good agreement between SCC-DFTB/MM (SCC-DFTB/CHARMM) and (B3LYP/6-31G*)/CHARMM (at single point energies). Moreover, in our mechanistic study of protein farnesyltransferase, good agreement (less than 2kcal/mol) between the calculated free energy barrier (using SCC-DFTB/AMBERff99SB) and experimentally measure energy barrier has been achieved[8]. Therefore, in this study we continue to use SCC-DFTB/MM to study the mechanism of NphB catalysis.

In practice, we only included two reactants, GPP and 1,6-DHN in our QM region. This selection not only allows for fast computation and a large amount of simulation, but also avoids potential problem caused by the lack of an implicit dispersion term. Dispersion has been a well-known problem for SCC-DFTB and an explicit dispersion correction term has been developed to improve simulation with SCC-DFTB[9,10]. However, such a term may cause problem using AMBER during long MD simulations and in particular restraint MD simulations such as SMD or US*. Hence, we decided to leave the sidechains from Lys119, Tyr121, Ser214, Tyr 216, Arg228, Lys284, Tyr288 in the MM region. Moreover, we left the $Mg^{2+}$ site in the MM region as well due to convergence issues. This resulted in a total of 56 atoms in the QM region and no link atoms were needed. In order to confirm that the AMBER force field ff99SB[11] models dispersion well, we made a comparison between 3 models in the US PMF study of 5-prenylation: in the

first model (MOD1), our normal QM-MM partition was applied, thus the interaction between geranyl moiety and Tyr121 would be handled exclusively by ff99SB; in the second model (MOD2), the sidechain of Tyr121 was included in the QM region (with the bond between $C_\alpha$ and $C_\beta$ being cut and a link atom introduced), in addition to GPP and 1,6-DHN while the explicit SCC-DFTB dispersion correction term was not applied; in the third model (MOD3), we applied the explicit dispersion correction to the same QM region selection as applied in MOD2. However, the third model failed to generate a complete free energy profile because the simulations failed to converge in the 1.5 to 2.2 Å windows*. Therefore, only the 2.2 to 4.0 Å region was compared across three models (see Figure S1). Clearly, the dispersion correction term is essential for the success of SCC-DFTB/MM to describe the interaction between Tyr121 and the geranyl moiety, as MOD2 overestimated the free energy barrier by approximately 3 kcal/mol while MOD3 and MOD1 predicted almost identical barrier height despite a discrepancy of less than 0.1 Å in the location of transition state. These results suggested that the QM/MM Lennard-Jones term from AMBER ff99SB is capable of handling the dispersion effect between QM and MM residues.

The biggest concern associated with semi-empirical theories is always their transferability. To address this, we also validated SCC-DFTB's performance on truncated systems, although the set of parameters we used were actually parameterized against phosphate hydrolysis reactions. We have successfully validated and shown that SCC-DFTB could predict the free energy barrier of a prenylation reaction successfully[8], therefore, the effort we report here will be focused on carbocation intermediate. We prepared a truncated system, including GPP, 1,6-DHN and two p-cresols, abstracted from

Tyr171 and Tyr216 by cleaving at $C_\alpha$ and filling the free valence site on $C_\beta$. Three states, the reactant state (RXT), the geranyl carbocation intermediate state (INT) and the prenylation product state (prenylated-1,6-DHN carbocation, PRO), were investigated. For each state, the truncated system was minimized (in the gas-phase) with SCC-DFTB using the SANDER module integrated in the AMBER11 package, followed by a HF/6-31G* minimization using QUICK[12] module in the same program and a single point calculation at the M06-2X/6-31+G** level using GAUSSIAN09. Then, three sets of results were collected and for each set, two values, $\Delta E_1 = E_{INT} - E_{RXT}$ and $\Delta E_2 = E_{INT} - E_{PRO}$, were calculated and compared. For $\Delta E_1$, the SCC-DFTB result (88.2 kcal/mol) is 3.5 kcal/mol lower than the HF result (91.7 kcal/mol) and 1.4 kcal/mol higher than the M06-2X single point result (86.8 kcal/mol); while for $\Delta E_2$, the SCC-DFTB result (5.3 kcal/mol) is 2.0 and 0.9 kcal/mol higher than the HF (3.3 kcal/mol) and M06-2X result (4.4 kcal/mol), respectively. On the other hand, the geometries of the truncated system from the SCC-DFTB and HF minimization are nearly identical. Therefore, we drew the conclusion that SCC-DFTB is capable of capturing the carbocation intermediate and predicting the associated free energy barrier.

Additionally, we also tested for the possibility of including another dimension in the reaction coordinate (RC), specifically the C-O bond. However, similar to the situation we have encountered as well as Klein and coworkers, including the additional RC results in unphysical dissociative pathway. Hence, we only employed the 1D RC (C-C) for this catalytic reaction. This conclusion should not generalized, in our opinion and should be tested in each individual case encountered.

In addition to the IEFPCM water model, the IEFPCM low dielectric (ε=4) model was applied to mimic the protein environment. The same trend as observed in the former case is reproduced, while the interaction energies are generally 1-3 kcal/mol more negative, meaning the interactions are more attractive. Although the interaction between GPP and DIN in P7 channel is attractive now, it is still much less attractive than in the other reaction channels (see Table S2).

*See http://structbio.vanderbilt.edu/archives/amber-archive/2009/2182.php.

## S3. Additional Figures

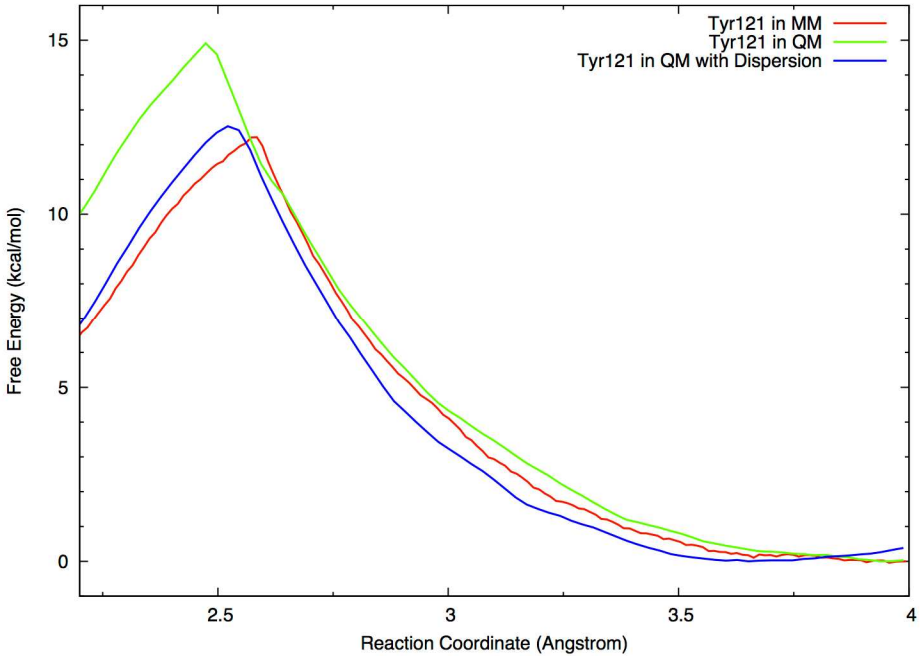


Figure S1. Method (QM selection) validation. (Red: MOD1. Green: MOD2. Blue: MOD3).

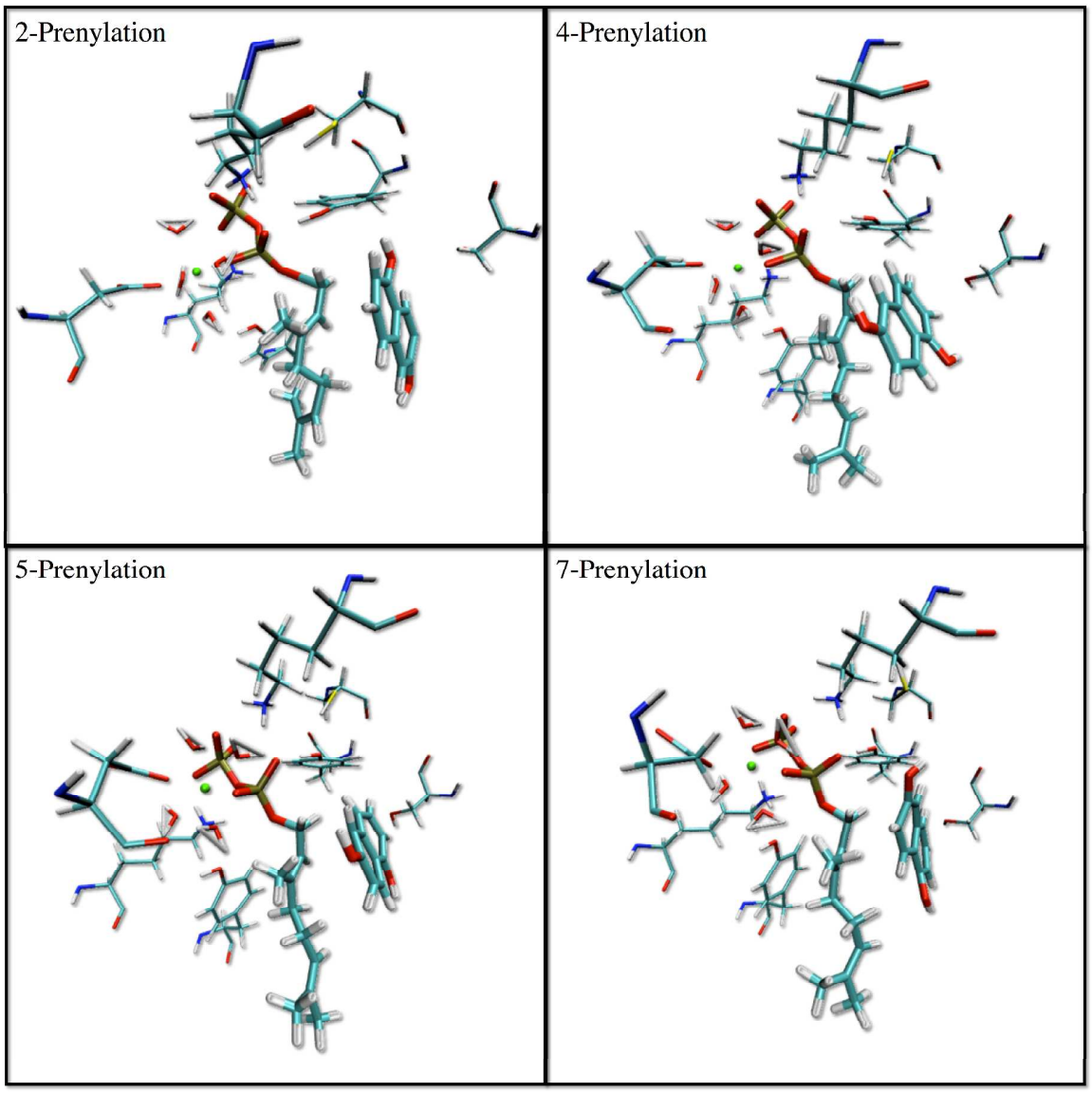


Figure S2. Snapshot of active site structures associated with rate-limiting transition state (TS1), corresponding to carbocation formation during prenylation step, for all 4 reaction channels.

**S4. Additional Tables**

| | P2-PCM | P4-PCM | P5-PCM | P7-PCM |
|---|---|---|---|---|
| Y121 (hartree) | -307.34 | -307.34 | -307.34 | -307.34 |
| Y216 (hartree) | -307.34 | -307.35 | -307.34 | -307.34 |
| DHN (hartree) | -536.12 | -536.13 | -536.12 | -536.12 |
| GPP (hartree) | -390.85 | -390.85 | -390.85 | -390.86 |
| GPP+Y121 (hartree) | -698.20 | -698.20 | -698.20 | -698.20 |
| GPP+Y216 (hartree) | -698.19 | -698.20 | -698.19 | -698.20 |
| GPP+DHN (hartree) | -927.00 | -926.99 | -926.99 | -926.97 |
| GPP-Y121 (kcal/mol) | -2.94 | -4.36 | -5.80 | -2.67 |
| GPP-Y216 (kcal/mol) | -0.70 | -1.34 | -0.67 | -0.53 |
| GPP-DHN (kcal/mol) | -20.57 | -6.82 | -13.35 | 0.99 |

Table S1. Complete M06-2X/6-31G** BSSE calculation results for the interaction energy of the "π-chamber" for the 4 possible prenylation products using IEFPCM water model. DHN = 1,6-DHN.

| | P2-PCM | P4-PCM | P5-PCM | P7-PCM |
|---|---|---|---|---|
| Y121 (hartree) | -307.34 | -307.34 | -307.34 | -307.34 |
| Y216 (hartree) | -307.33 | -307.34 | -307.34 | -307.34 |
| DIN (hartree) | -536.12 | -536.12 | -536.11 | -536.11 |
| GPP+Y121 (hartree) | -698.18 | -698.18 | -698.18 | -698.18 |
| GPP+Y216 (hartree) | -698.17 | -698.18 | -698.17 | -698.18 |
| GPP+DIN (hartree) | -926.99 | -926.97 | -926.97 | -926.95 |
| GPP (hartree) | -390.83 | -390.83 | -390.83 | -390.84 |
| GPP-Y121 (kcal/mol) | -4.48 | -6.18 | -7.35 | -4.20 |
| GPP-Y216 (kcal/mol) | -1.96 | -2.62 | -1.43 | -1.65 |
| GPP-DIN (kcal/mol) | -23.85 | -9.65 | -16.50 | -2.45 |

Table S2. Complete M06-2X/6-31G** BSSE calculation results for the interaction energy of the "π-chamber" for the 4 possible prenylation products using IEFPCM low dielectric water model (ε=4). DHN = 1,6-DHN.

## S5. Gaussian Input Structures

P2:

| | | | |
|---|---|---|---|
| C | 52.26100000 | 40.79300000 | 29.21000000 |
| C | 53.10300000 | 39.94800000 | 28.46200000 |
| C | 54.14000000 | 39.21100000 | 29.07400000 |
| C | 54.15000000 | 38.96200000 | 30.55700000 |
| C | 55.23600000 | 38.53400000 | 28.29200000 |
| C | 55.38200000 | 36.99200000 | 28.43100000 |
| C | 56.81400000 | 36.65000000 | 28.01700000 |
| C | 57.83500000 | 36.40900000 | 28.89500000 |
| C | 57.50900000 | 36.13500000 | 30.34200000 |
| C | 59.22000000 | 36.29200000 | 28.41500000 |
| H | 51.42800000 | 41.23900000 | 28.76400000 |
| H | 52.43900000 | 40.87800000 | 30.20900000 |
| H | 53.13200000 | 39.93000000 | 27.34600000 |
| H | 54.14000000 | 39.87700000 | 31.04900000 |
| H | 54.97700000 | 38.28400000 | 30.75200000 |
| H | 53.16300000 | 38.43100000 | 30.75700000 |
| H | 55.30900000 | 38.68700000 | 27.21100000 |
| H | 56.19100000 | 38.94700000 | 28.73900000 |
| H | 55.27900000 | 36.68500000 | 29.50500000 |
| H | 54.58800000 | 36.54700000 | 27.81900000 |
| H | 57.09200000 | 36.70200000 | 26.97900000 |
| H | 57.17200000 | 37.08900000 | 30.86600000 |
| H | 58.36300000 | 35.69300000 | 30.89500000 |
| H | 56.66200000 | 35.37100000 | 30.34300000 |
| H | 59.84800000 | 37.09100000 | 28.74700000 |
| H | 59.26000000 | 36.42700000 | 27.30300000 |
| H | 59.60000000 | 35.31100000 | 28.76700000 |
| C | 55.42300000 | 41.85600000 | 27.63300000 |
| C | 56.42300000 | 41.27700000 | 26.84200000 |
| C | 56.18400000 | 41.11600000 | 25.42200000 |
| C | 55.05800000 | 41.69200000 | 24.83300000 |
| C | 54.06600000 | 42.23000000 | 25.63800000 |
| C | 53.25500000 | 42.97500000 | 27.88600000 |
| C | 54.50200000 | 42.31900000 | 29.88600000 |
| C | 55.57100000 | 41.83700000 | 29.05600000 |
| O | 52.30600000 | 43.71000000 | 27.34700000 |
| O | 57.09600000 | 40.50800000 | 24.64600000 |
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| C | 54.20300000 | 42.31800000 | 27.04100000 |
| H | 57.43800000 | 41.05800000 | 27.20600000 |
| H | 54.89200000 | 41.53800000 | 23.77400000 |
| H | 53.14700000 | 42.60100000 | 25.14600000 |
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| C | 53.02700000 | 33.86400000 | 27.18400000 |
| C | 53.36700000 | 33.63600000 | 28.56400000 |
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| C | 52.03400000 | 35.53000000 | 29.19600000 |
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| H | 51.57800000 | 35.94700000 | 31.04100000 |
| C | 51.71100000 | 35.81200000 | 27.88400000 |
| H | 50.96600000 | 36.57400000 | 27.70700000 |
| C | 52.27500000 | 35.00800000 | 26.88800000 |
| H | 52.11300000 | 35.33100000 | 25.87000000 |
| C | 47.97500000 | 41.44000000 | 23.99600000 |
| C | 47.13300000 | 40.96000000 | 25.00800000 |
| H | 46.33300000 | 40.26300000 | 24.80700000 |
| C | 47.28400000 | 41.38500000 | 26.39100000 |
| H | 46.71400000 | 41.03200000 | 27.23700000 |
| C | 48.43600000 | 42.17600000 | 26.65300000 |
| O | 48.76100000 | 42.45600000 | 27.94800000 |
| H | 48.43900000 | 41.86600000 | 28.63400000 |
| C | 49.33000000 | 42.64400000 | 25.55900000 |
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P4:

| | | | |
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| C | 55.59100000 | 35.02300000 | 30.62900000 |
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| H | 54.31700000 | 34.15800000 | 32.06200000 |
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| C | 54.42880619 | 39.97248115 | 30.55331700 |
| C | 53.25580619 | 39.65148115 | 28.37831700 |
| C | 50.90280619 | 40.38148115 | 28.22531700 |
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| C | 45.42800000 | 39.62500000 | 27.26700000 |
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| H | 46.15089639 | 39.74584296 | 25.23077300 |

P5:

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| C | 55.62129337 | 41.17500423 | 29.59669555 |
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| C | 52.86129337 | 42.20800423 | 25.48669555 |
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| H | 56.66000000 | 41.19500000 | 30.23700000 |
| H | 56.69829337 | 40.60200423 | 27.85769555 |
| H | 52.10529337 | 42.47200423 | 24.78169555 |
| H | 51.59229337 | 42.46900423 | 27.23069555 |
| H | 56.07129337 | 40.40400423 | 24.49969555 |
| H | 53.26529337 | 41.73700423 | 31.65369555 |
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| C | 52.96300000 | 33.73300000 | 27.25300000 |
| C | 53.24900000 | 33.60900000 | 28.62300000 |
| H | 53.86500000 | 32.78700000 | 28.95700000 |
| C | 52.69900000 | 34.44600000 | 29.56800000 |
| H | 52.94300000 | 34.35700000 | 30.61600000 |
| C | 51.84300000 | 35.50400000 | 29.22700000 |
| O | 51.25000000 | 36.27300000 | 30.16500000 |
| H | 51.42200000 | 35.80900000 | 30.98700000 |
| C | 51.58600000 | 35.66400000 | 27.86500000 |
| H | 50.89200000 | 36.44100000 | 27.58100000 |
| C | 52.15400000 | 34.87000000 | 26.86500000 |
| H | 51.91600000 | 35.09500000 | 25.83600000 |
| C | 47.95000000 | 41.30900000 | 23.75400000 |
| C | 47.35000000 | 40.62300000 | 24.83900000 |
| H | 46.73600000 | 39.77600000 | 24.57000000 |
| C | 47.70000000 | 40.92400000 | 26.21100000 |
| H | 47.40500000 | 40.41400000 | 27.11600000 |
| C | 48.51200000 | 42.03500000 | 26.49800000 |
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| H | 48.77800000 | 41.45900000 | 28.26100000 |
| C | 49.04000000 | 42.75900000 | 25.41800000 |
| H | 49.68600000 | 43.60200000 | 25.61200000 |
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| H | 49.25600000 | 42.99700000 | 23.29400000 |
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P7:

| | | | |
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| C | 53.32000000 | 39.09200000 | 30.15200000 |
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| C | 54.38600000 | 38.05800000 | 30.04000000 |
| C | 55.67800000 | 38.74900000 | 30.52300000 |
| C | 56.83300000 | 38.01100000 | 29.85600000 |
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| C | 57.68000000 | 36.78800000 | 31.88600000 |
| C | 58.69000000 | 36.45300000 | 29.59900000 |
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| H | 53.26800000 | 39.40100000 | 28.03100000 |
| H | 52.95900000 | 38.56000000 | 32.24600000 |
| H | 51.92800000 | 39.91100000 | 31.67800000 |
| H | 53.67900000 | 40.25100000 | 31.87500000 |
| H | 54.23400000 | 37.12500000 | 30.63600000 |
| H | 54.52300000 | 37.77300000 | 28.98100000 |
| H | 55.60000000 | 39.80400000 | 30.16500000 |
| H | 55.71300000 | 38.78200000 | 31.65100000 |
| H | 57.15800000 | 38.20300000 | 28.80000000 |
| H | 58.68600000 | 36.96600000 | 32.30300000 |
| H | 57.47800000 | 35.76000000 | 32.10300000 |
| H | 56.96000000 | 37.47400000 | 32.42400000 |
| H | 58.59900000 | 36.80300000 | 28.61700000 |
| H | 58.49000000 | 35.37200000 | 29.59400000 |
| H | 59.72300000 | 36.60000000 | 29.94500000 |
| C | 53.35012996 | 42.62501132 | 26.41658253 |
| C | 52.38512996 | 43.28401132 | 27.14758253 |
| C | 52.25912996 | 43.26501132 | 28.51858253 |
| C | 53.22712996 | 42.50101132 | 29.34858253 |
| C | 54.11412996 | 41.76101132 | 28.55358253 |
| C | 55.24412996 | 41.11101132 | 26.43958253 |
| C | 54.20212996 | 41.86601132 | 24.32858253 |
| C | 53.27812996 | 42.58801132 | 25.00458253 |
| O | 56.18912996 | 40.50301132 | 27.14758253 |
| O | 51.23712996 | 43.90301132 | 29.17458253 |
| C | 55.19112996 | 41.09201132 | 25.04658253 |
| C | 54.24612996 | 41.85801132 | 27.12758253 |
| H | 51.57412996 | 43.78501132 | 26.54058253 |
| H | 53.19412996 | 42.61101132 | 30.45958253 |
| H | 54.97212996 | 41.29301132 | 29.06458253 |
| H | 54.04612996 | 41.76801132 | 23.26058253 |
| H | 52.53712996 | 43.11801132 | 24.52258253 |
| H | 56.84412996 | 40.01901132 | 26.60858253 |
| H | 50.76612996 | 44.53201132 | 28.55258253 |
| H | 55.83712996 | 40.46801132 | 24.43858253 |
| C | 52.76600000 | 33.51000000 | 27.86400000 |
| C | 52.67200000 | 33.26100000 | 29.27700000 |
| H | 53.10800000 | 32.34600000 | 29.65200000 |
| C | 52.22800000 | 34.19500000 | 30.18500000 |
| H | 52.24900000 | 34.07300000 | 31.25800000 |
| C | 51.76500000 | 35.45900000 | 29.71000000 |
| O | 51.20300000 | 36.34800000 | 30.65000000 |
| H | 51.19900000 | 36.01500000 | 31.55100000 |
| C | 51.81300000 | 35.74700000 | 28.35000000 |
| H | 51.42900000 | 36.65200000 | 27.90300000 |
| C | 52.38800000 | 34.83100000 | 27.46400000 |
| H | 52.60300000 | 35.02900000 | 26.42400000 |
| C | 47.55600000 | 41.59500000 | 24.31000000 |
| C | 46.82800000 | 41.06100000 | 25.40500000 |
| H | 46.05900000 | 40.33200000 | 25.19500000 |
| C | 47.14200000 | 41.40400000 | 26.76300000 |
| H | 46.63800000 | 40.87700000 | 27.56000000 |
| C | 48.13800000 | 42.37500000 | 26.99400000 |
| O | 48.50700000 | 42.58800000 | 28.25800000 |
| H | 48.21000000 | 41.91800000 | 28.87800000 |
| C | 48.85100000 | 43.00400000 | 25.90000000 |
| H | 49.56900000 | 43.79200000 | 26.07300000 |
| C | 48.52100000 | 42.57400000 | 24.58500000 |
| H | 49.14100000 | 42.98300000 | 23.80100000 |
| H | 53.09259703 | 32.76672451 | 27.16702373 |
| H | 47.37465097 | 41.26199119 | 23.30944133 |

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