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Highly diastereoselective amplification from a dynamic combinatorial library of macrocyclic oligoamines

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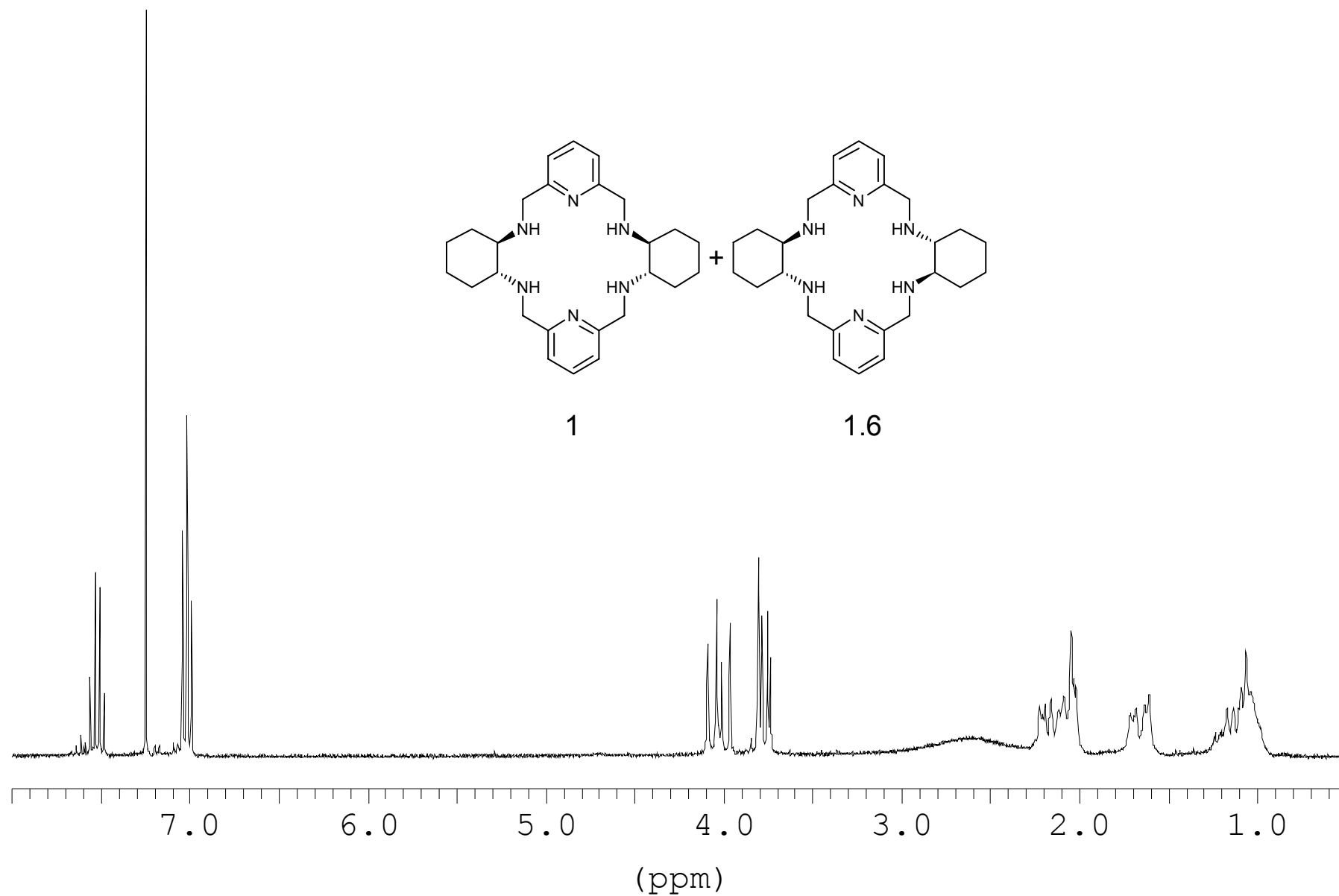
E-mail: ialfonso@qio.uji.es and vgs@fq.uniovi.es

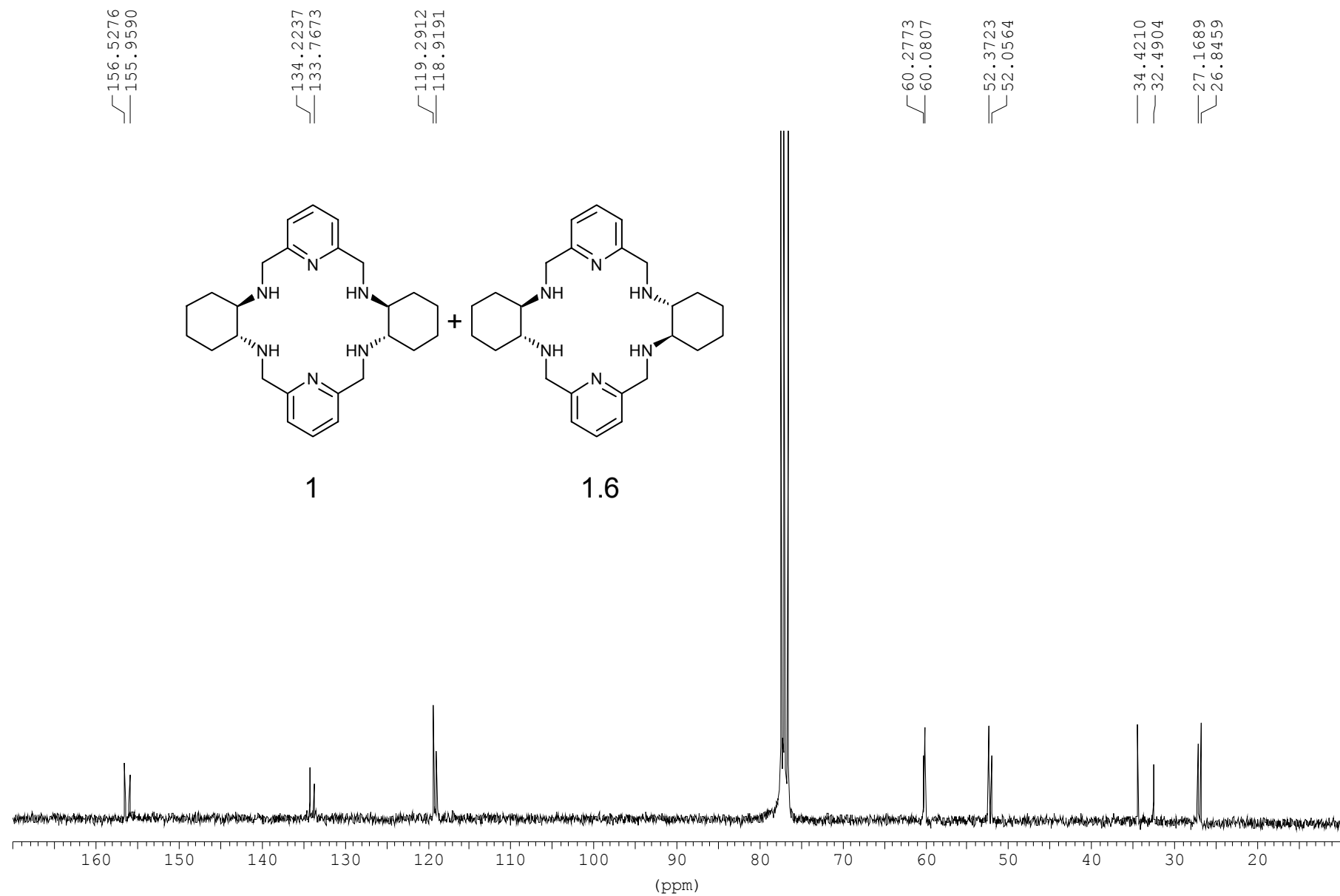
Racemic Dynamic Combinatorial Library templated with Ba(II)

A mixture of racemic *trans*-cyclohexane-1,2-diamine (*rac*-**1**, 30 μ l, 0.25 mmol) and pyridine-2,6-dicarboxaldehyde (**2**, 34 mg, 0.25 mmol) in dry MeOH (5 ml, 0.05 M final concentration each) was stirred under nitrogen for 3 hours and a precipitate was formed. After this time, BaCl₂ (92 mg, 0.375 mmol) was added and the reaction mixture was stirred until the precipitate was redissolved (15 days). An excess of NaBH₄ (40 mg, 1 mmol) was then added carefully at 0°C. Next, the mixture was reacted for 5 hours at room temperature before being hydrolyzed (conc. HCl to acidity) and evaporated to dryness. The residue obtained was extracted thoroughly with NaOH (1 N) and CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated in vacuo to give rise to the final polyamines.

ESI-MS (positive scan, MeOH:H₂O 90:10, 350 °C) spectrum showed the peaks (*m/z*, %): 435 (100%) [M+H]⁺, 457 (13%) [M+Na]⁺, 218.3 (27%) [M+2H]²⁺.

Attached are the corresponding ¹H NMR (300 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) spectra.



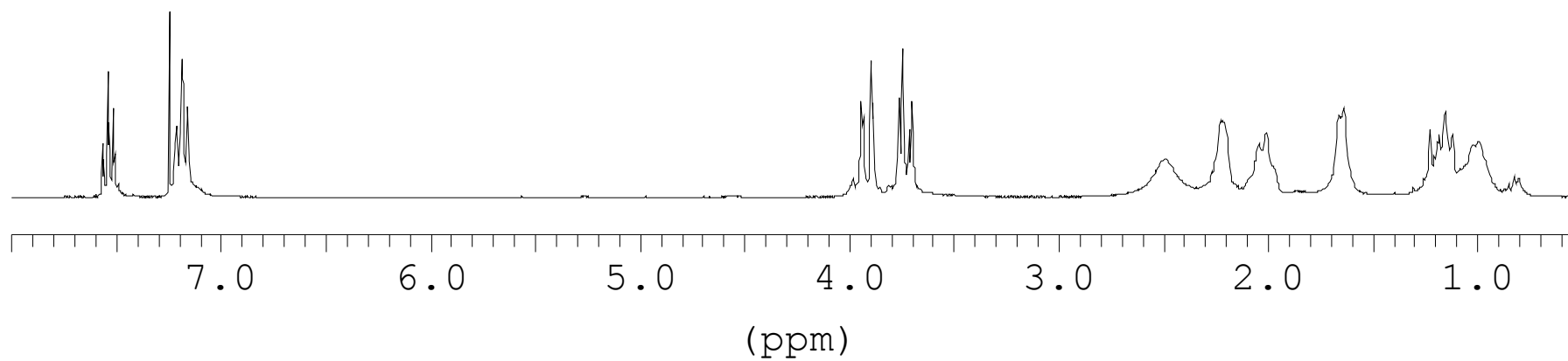
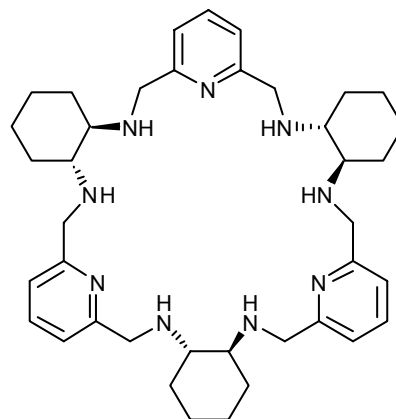


Racemic Dynamic Combinatorial Library templated with Cd(II)

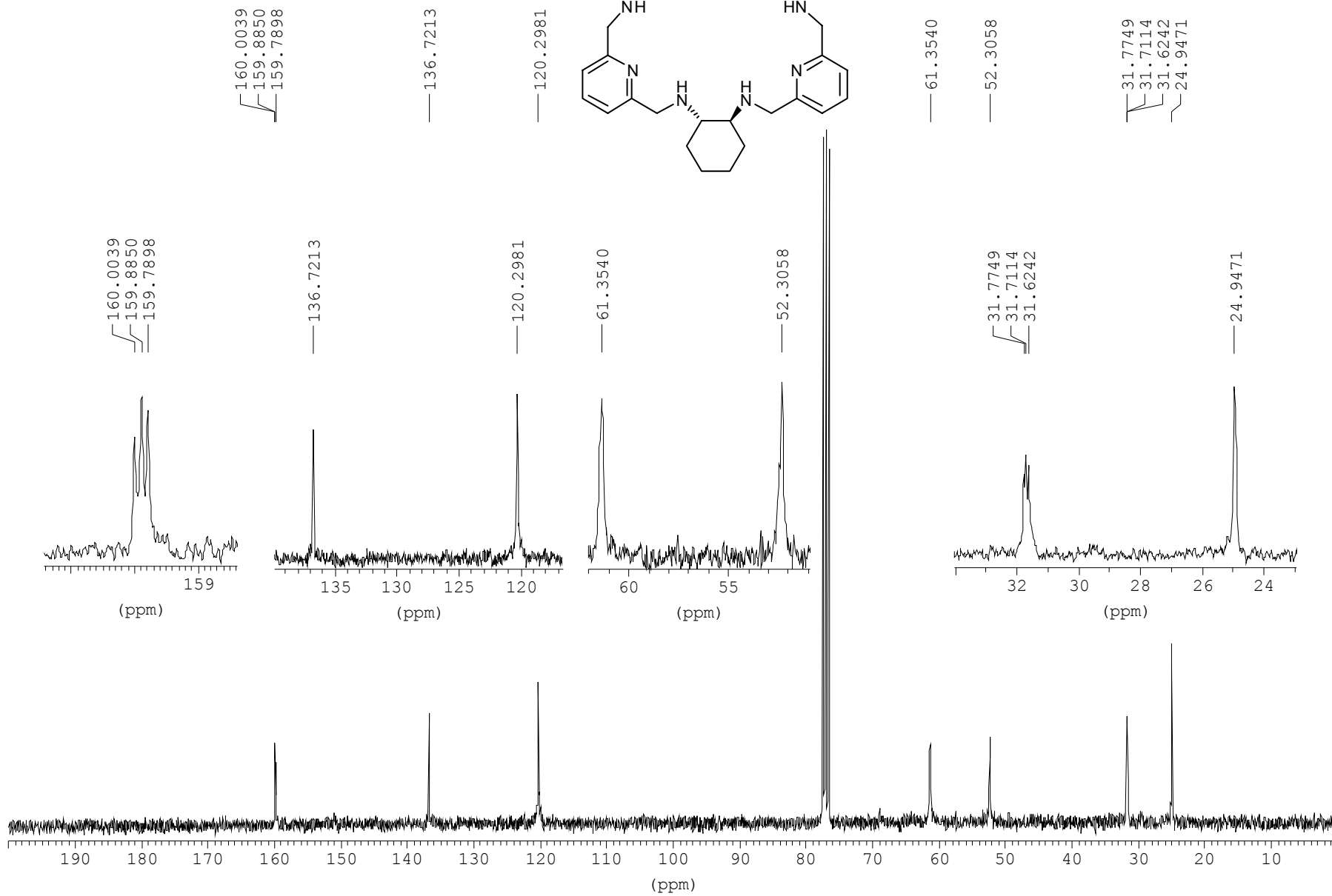
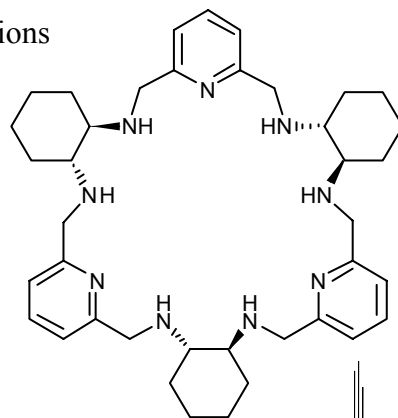
A mixture of racemic *trans*-cyclohexane-1,2-diamine (*rac*-**1**, 60 μ l, 0.5 mmol) and pyridine-2,6-dicarboxaldehyde (**2**, 68 mg, 0.5 mmol) in dry MeOH (10 ml, 0.05 M final concentration each) was stirred under nitrogen for 3 hours and a precipitate was formed. After this time, CdCl₂ (275 mg, 1.5 mmol) was added and the reaction mixture was stirred during 18 hours to permit the system to equilibrate. The precipitate was redissolved. An excess of NaBH₄ (80 mg, 2.1 mmol) was then added carefully at 0°C. Next, the mixture was reacted for 5 hours at room temperature before being hydrolyzed (conc. HCl to acidity) and evaporated to dryness. The residue obtained was continuously extracted with NaOH (1 N) and CH₂Cl₂ overnight. The organic layer was dried (Na₂SO₄) and the solvent was evaporated in vacuo to give rise to the final compound hetero-**7** as a white solid.

ESI-MS (positive scan, MeOH:H₂O 90:10, 350 °C) spectrum showed the peaks (*m/z*, %): 652 (100%) [M+H]⁺, 674 (27%) [M+Na]⁺, 326.7 (7%) [M+2H]²⁺.

Attached are the corresponding ¹H (300 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) spectra.



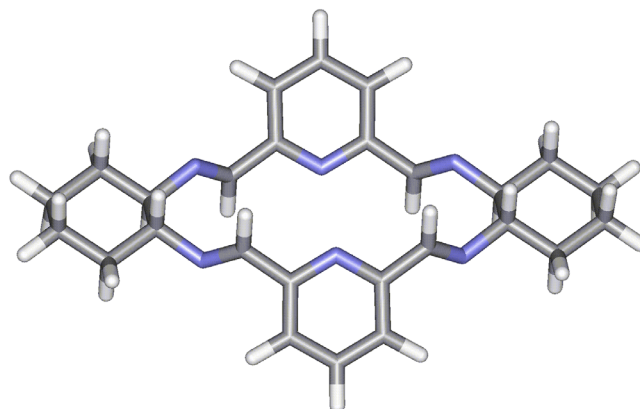
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Molecular modeling.

All the theoretical calculations were performed using Spartan '04 program. The optimized geometries obtained for each diastereomeric complex were fully minimized using the PM3 semiempirical quantum mechanics calculations (see Figure 3 in manuscript). Frequencies analyses showed that all the structures were minima of energy.

Cartesian coordinates and energies for the optimized minima



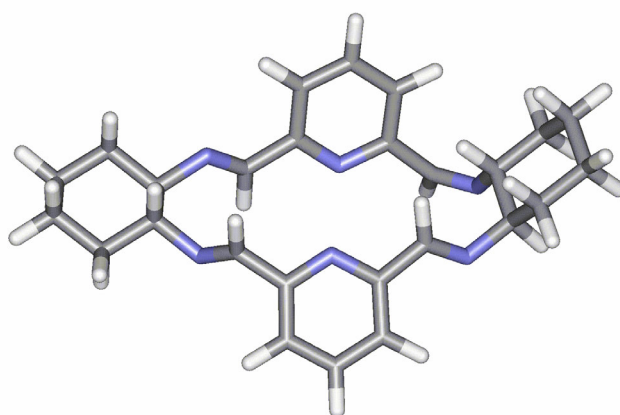
Hetero-3

E (PM3) = 114.652 Kcal/mol

62

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H	0.397500	7.251000	-0.300000
H	-1.154500	7.913000	-0.824000
C	-0.167500	6.689000	-2.313000
H	0.377500	7.539000	-2.766000
H	-1.092500	6.569000	-2.911000
C	0.678500	5.428000	-2.401000
H	1.654500	5.593000	-1.901000
H	0.914500	5.208000	-3.460000
C	-0.058500	4.242000	-1.765000
H	-1.018500	4.070000	-2.323000
C	-0.384500	4.570000	-0.282000
H	0.574500	4.753000	0.273000
C	-1.244500	5.839000	-0.217000
H	-1.481500	6.086000	0.837000
H	-2.220500	5.673000	-0.716000
N	0.820500	3.056000	-1.816000
N	-1.147500	3.450000	0.305000
C	0.410500	1.937000	-2.308000
H	-0.595500	1.786000	-2.734000
C	-0.644500	2.706000	1.230000
H	0.362500	2.855000	1.657000
C	-1.408500	1.533000	1.703000
C	-2.671500	-0.798000	2.471000
C	-2.789500	1.545000	1.927000
N	-0.674500	0.403000	1.882000
C	-1.293500	-0.754000	2.234000
C	-3.416500	0.369000	2.327000

H	-3.366500	2.464000	1.777000
H	-4.495500	0.357000	2.513000
H	-3.154500	-1.740000	2.753000
C	1.293500	0.754000	-2.234000
C	2.790500	-1.545000	-1.928000
C	2.672500	0.798000	-2.472000
N	0.675500	-0.403000	-1.882000
C	1.408500	-1.533000	-1.703000
C	3.416500	-0.369000	-2.329000
H	3.154500	1.740000	-2.754000
H	4.495500	-0.358000	-2.515000
H	3.366500	-2.464000	-1.778000
C	0.644500	-2.706000	-1.229000
H	-0.362500	-2.854000	-1.656000
C	-0.410500	-1.937000	2.308000
H	0.596500	-1.786000	2.734000
N	1.148500	-3.450000	-0.305000
N	-0.820500	-3.056000	1.817000
C	0.385500	-4.570000	0.282000
H	-0.573500	-4.753000	-0.273000
C	0.059500	-4.242000	1.765000
H	1.019500	-4.070000	2.323000
C	1.246500	-5.839000	0.217000
H	2.222500	-5.672000	0.716000
H	1.483500	-6.086000	-0.836000
C	0.523500	-7.007000	0.870000
H	1.156500	-7.913000	0.825000
H	-0.395500	-7.251000	0.300000
C	0.168500	-6.689000	2.313000
H	1.094500	-6.569000	2.912000
H	-0.375500	-7.539000	2.766000
C	-0.676500	-5.428000	2.401000
H	-0.913500	-5.208000	3.460000
H	-1.653500	-5.593000	1.901000



Homo-3

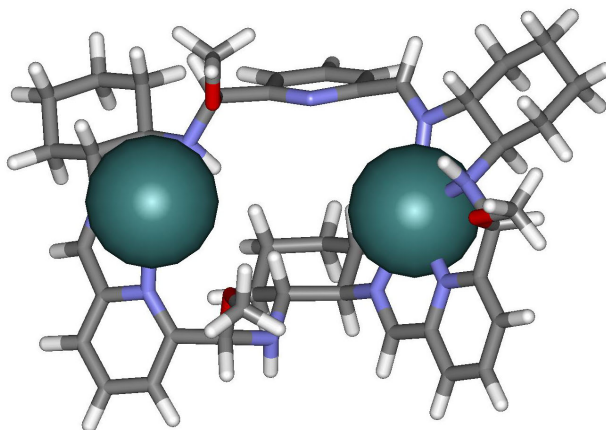
E (PM3) = 115.792 Kcal/mol

62

C	-0.454500	6.367500	-0.954000
H	0.442500	6.625500	-0.356000
H	-1.081500	7.278500	-0.965000
C	-0.043500	6.000500	-2.371000
H	0.533500	6.829500	-2.824000

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H	-0.944500	5.878500	-3.005000
C	0.784500	4.724500	-2.391000
H	1.743500	4.886500	-1.859000
H	1.056500	4.469500	-3.433000
C	0.000500	3.573500	-1.749000
H	-0.949500	3.415500	-2.329000
C	-0.358500	3.954500	-0.286000
H	0.587500	4.154500	0.285000
C	-1.212500	5.227500	-0.290000
H	-1.484500	5.510500	0.745000
H	-2.171500	5.052500	-0.818000
N	0.839500	2.356500	-1.753000
N	-1.128500	2.843500	0.310000
C	0.366500	1.227500	-2.160000
H	-0.663500	1.104500	-2.540000
C	-0.671500	2.179500	1.315000
H	0.273500	2.415500	1.833000
C	-1.383500	0.955500	1.741000
C	-2.529500	-1.475500	2.364000
C	-2.736500	0.911500	2.094000
N	-0.619500	-0.165500	1.724000
C	-1.181500	-1.371500	2.005000
C	-3.301500	-0.318500	2.419000
H	-3.338500	1.826500	2.099000
H	-4.357500	-0.377500	2.702000
H	-2.969500	-2.454500	2.585000
C	1.192500	0.006500	-2.074000
C	2.546500	-2.392500	-1.866000
C	2.589500	0.011500	-1.985000
N	0.494500	-1.162500	-2.071000
C	1.149500	-2.343500	-1.952000
C	3.264500	-1.201500	-1.888000
H	3.140500	0.959500	-1.987000
H	4.357500	-1.218500	-1.825000
H	3.064500	-3.356500	-1.790000
C	0.301500	-3.556500	-1.974000
H	-0.404500	-3.649500	-2.813000
C	-0.262500	-2.517500	1.864000
H	0.813500	-2.301500	1.988000
N	0.258500	-4.515500	-1.122000
N	-0.720500	-3.683500	1.556000
C	1.087500	-4.635500	0.093000
C	0.164500	-4.841500	1.324000
H	-0.542500	-5.684500	1.123000
H	1.721500	-3.722500	0.257000
C	2.007500	-5.850500	-0.099000
H	2.694500	-5.669500	-0.950000
H	1.412500	-6.746500	-0.373000
C	2.811500	-6.137500	1.157000
H	3.461500	-7.018500	0.995000
H	3.496500	-5.293500	1.375000
C	1.887500	-6.377500	2.337000
H	2.477500	-6.593500	3.248000
H	1.266500	-7.278500	2.157000
C	0.998500	-5.169500	2.572000
H	0.329500	-5.359500	3.433000
H	1.625500	-4.299500	2.861000



E (PM3) = 953.124 Kcal/mol

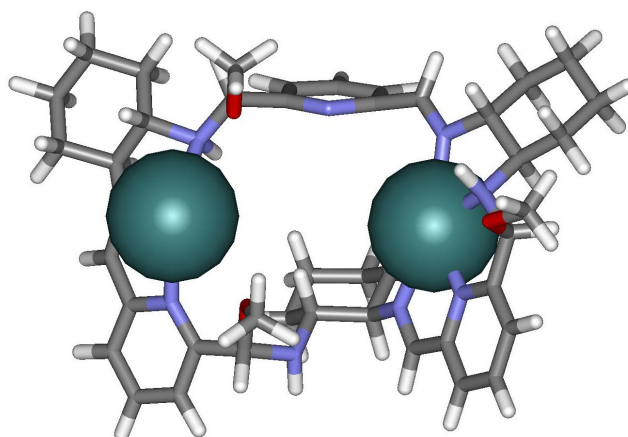
113

C	-5.941000	-1.249500	-2.030000
N	-4.760000	-1.380500	-1.305000
C	-4.222000	-2.629500	-1.188000
O	-2.540000	-1.941500	0.442000
O	-2.476000	3.173500	-0.024000
N	2.996000	2.138500	-0.380000
Cd	2.458000	-0.201500	-0.381000
N	1.180000	-2.014500	-1.459000
C	4.223000	2.408500	0.484000
C	4.949000	1.098500	0.876000
O	4.203000	-1.068500	3.457000
C	1.533000	-3.222500	-1.105000
Cd	-4.345000	0.811500	-0.219000
H	3.849000	2.912500	1.416000
H	5.344000	0.586500	-0.043000
H	1.130000	-4.138500	-1.576000
C	-2.219000	-2.496500	1.706000
H	-1.332000	-3.138500	1.655000
H	-3.059000	-3.056500	2.132000
H	-2.009000	-1.609500	2.308000
C	-2.846000	-2.902500	-0.559000
H	-2.889000	-3.938500	-0.121000
C	-4.918000	-3.764500	-1.655000
H	-4.483000	-4.767500	-1.522000
C	-6.153000	-3.632500	-2.270000
H	-6.717000	-4.519500	-2.600000
C	-6.663000	-2.347500	-2.490000
H	-7.614000	-2.211500	-3.028000
N	-1.690000	-2.948500	-1.502000
H	-1.826000	-3.698500	-2.150000
N	3.960000	0.134500	1.501000
H	3.492000	0.613500	2.255000
C	6.130000	1.429500	1.801000
H	6.652000	0.484500	2.079000
H	5.766000	1.868500	2.754000
C	7.104000	2.381500	1.129000
H	7.933000	2.619500	1.825000
H	7.581000	1.893500	0.254000
C	6.398000	3.657500	0.705000
H	6.051000	4.221500	1.595000
H	7.109000	4.329500	0.184000

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C	5.229000	3.342500	-0.213000
H	5.600000	2.884500	-1.152000
H	4.721000	4.288500	-0.509000
C	2.540000	-3.404500	-0.046000
C	4.465000	-3.641500	1.920000
C	2.931000	-4.674500	0.375000
N	3.096000	-2.261500	0.494000
C	4.033000	-2.380500	1.472000
C	3.913000	-4.789500	1.367000
H	2.483000	-5.575500	-0.069000
H	4.242000	-5.784500	1.705000
H	5.232000	-3.711500	2.707000
C	1.285000	3.309500	-1.782000
C	-0.881000	4.017500	-3.315000
C	1.496000	3.766500	-3.090000
N	0.035000	3.159500	-1.266000
C	-1.040000	3.534500	-2.008000
C	0.392000	4.107500	-3.868000
H	2.512000	3.892500	-3.488000
H	0.530000	4.479500	-4.894000
H	-1.755000	4.355500	-3.898000
C	-2.297000	4.251500	0.881000
H	-1.328000	4.741500	0.740000
H	-2.332000	3.754500	1.854000
H	-3.105000	4.987500	0.794000
C	-2.439000	3.534500	-1.395000
H	-2.902000	4.554500	-1.545000
C	5.244000	-1.108500	4.412000
H	5.918000	-0.248500	4.314000
H	5.811000	-2.044500	4.353000
H	4.691000	-1.056500	5.355000
C	4.603000	-1.110500	2.099000
H	5.725000	-1.083500	1.962000
C	-6.358000	0.110500	-2.435000
H	-7.103000	0.202500	-3.250000
N	-5.783000	1.127500	-1.856000
C	2.462000	3.213500	-0.890000
H	2.935000	4.207500	-0.700000
N	-3.325000	2.448500	-1.966000
H	-2.739000	1.822500	-2.501000
C	-5.835000	2.542500	-2.332000
H	-6.014000	3.140500	-1.399000
C	-4.436000	2.879500	-2.932000
H	-4.290000	2.262500	-3.859000
C	-4.404000	4.354500	-3.350000
H	-3.443000	4.578500	-3.867000
H	-4.421000	5.009500	-2.449000
C	-5.547000	4.699500	-4.291000
H	-5.407000	4.184500	-5.263000
H	-5.517000	5.784500	-4.523000
C	-6.895000	4.337500	-3.696000
H	-7.703000	4.572500	-4.419000
H	-7.109000	4.958500	-2.802000
C	-6.938000	2.859500	-3.343000
H	-6.822000	2.253500	-4.266000
H	-7.933000	2.603500	-2.926000
C	-1.249000	-1.723500	-2.231000
H	-1.383000	-0.849500	-1.547000
C	0.253000	-1.844500	-2.626000
H	0.365000	-2.719500	-3.323000
C	0.719000	-0.573500	-3.355000

H	1.766000	-0.696500	-3.703000
H	0.738000	0.284500	-2.640000
C	-0.148000	-0.242500	-4.558000
H	0.174000	0.721500	-5.000000
H	0.012000	-0.999500	-5.355000
C	-1.620000	-0.189500	-4.193000
H	-1.833000	0.674500	-3.520000
H	-2.225000	-0.013500	-5.105000
C	-2.041000	-1.489500	-3.530000
H	-3.129000	-1.472500	-3.328000
H	-1.889000	-2.333500	-4.237000



E (PM3) = 949.886 Kcal/mol

113

C	-5.710500	-1.563000	-2.232000
N	-4.576500	-1.734000	-1.441000
C	-4.032500	-2.984000	-1.374000
O	-2.430500	-2.322000	0.349000
O	-2.256500	2.787000	0.582000
N	3.103500	1.706000	-0.399000
Cd	2.606500	-0.663000	-0.338000
N	1.379500	-2.555000	-1.360000
C	4.400500	1.982000	0.354000
C	5.114500	0.675000	0.771000
O	4.433500	-1.284000	3.535000
C	1.714500	-3.733000	-0.903000
Cd	-4.209500	0.347000	-0.214000
H	4.113500	2.549000	1.281000
H	5.436500	0.100000	-0.139000
H	1.330500	-4.681000	-1.325000
C	-2.098500	-2.855000	1.620000
H	-1.207500	-3.491000	1.575000
H	-2.932500	-3.415000	2.059000
H	-1.892500	-1.957000	2.207000
C	-2.721500	-3.305000	-0.637000
H	-2.862500	-4.315000	-0.161000
C	-4.670500	-4.087000	-1.980000
H	-4.231500	-5.094000	-1.886000
C	-5.855500	-3.923000	-2.677000
H	-6.375500	-4.787000	-3.120000
C	-6.374500	-2.631000	-2.830000
H	-7.288500	-2.467000	-3.422000
N	-1.503500	-3.449000	-1.486000

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H	-1.606500	-4.256000	-2.069000
N	4.139500	-0.224000	1.506000
H	3.702500	0.316000	2.237000
C	6.361500	1.027000	1.598000
H	6.875500	0.087000	1.904000
H	6.071500	1.535000	2.542000
C	7.312500	1.905000	0.803000
H	8.192500	2.160000	1.427000
H	7.715500	1.350000	-0.068000
C	6.615500	3.175000	0.346000
H	6.348500	3.806000	1.218000
H	7.307500	3.789000	-0.265000
C	5.375500	2.844000	-0.468000
H	5.664500	2.323000	-1.403000
H	4.868500	3.785000	-0.781000
C	2.681500	-3.844000	0.201000
C	4.572500	-3.963000	2.209000
C	3.038500	-5.084000	0.728000
N	3.248500	-2.672000	0.661000
C	4.175500	-2.733000	1.655000
C	4.000500	-5.139000	1.744000
H	2.581500	-6.008000	0.346000
H	4.301500	-6.111000	2.167000
H	5.329500	-3.985000	3.009000
C	1.268500	2.904000	-1.618000
C	-1.051500	3.709000	-2.852000
C	1.319500	3.338000	-2.948000
N	0.092500	2.813000	-0.938000
C	-1.053500	3.235000	-1.531000
C	0.137500	3.730000	-3.573000
H	2.277500	3.412000	-3.482000
H	0.153500	4.093000	-4.611000
H	-1.971500	4.100000	-3.310000
C	-2.001500	3.742000	1.598000
H	-1.046500	4.254000	1.442000
H	-1.957500	3.122000	2.497000
H	-2.813500	4.475000	1.676000
C	-2.348500	3.316000	-0.725000
H	-2.680500	4.399000	-0.722000
C	5.508500	-1.257000	4.452000
H	6.185500	-0.415000	4.258000
H	6.065500	-2.200000	4.449000
H	4.991500	-1.122000	5.407000
C	4.783500	-1.432000	2.171000
H	5.899500	-1.438000	1.993000
C	-6.152500	-0.187000	-2.545000
H	-6.868500	-0.050000	-3.378000
N	-5.625500	0.804000	-1.880000
C	2.539500	2.784000	-0.870000
H	3.053500	3.769000	-0.748000
N	-3.430500	2.425000	-1.320000
H	-3.128500	2.177000	-2.247000
C	-5.751500	2.227000	-2.320000
H	-5.421500	2.265000	-3.394000
C	-7.170500	2.800000	-2.226000
H	-7.536500	2.787000	-1.179000
C	-7.174500	4.224000	-2.766000
H	-8.192500	4.653000	-2.667000
H	-6.959500	4.220000	-3.855000
C	-6.172500	5.102000	-2.034000
H	-6.495500	5.262000	-0.985000

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H	-6.153500	6.111000	-2.494000
C	-4.773500	4.503000	-2.065000
H	-4.068500	5.156000	-1.501000
H	-4.389500	4.471000	-3.106000
C	-4.794500	3.097000	-1.452000
H	-5.182500	3.171000	-0.399000
C	-0.997500	-2.302000	-2.297000
H	-1.150500	-1.367000	-1.704000
C	0.520500	-2.489000	-2.590000
H	0.646500	-3.434000	-3.185000
C	1.057500	-1.316000	-3.426000
H	2.125500	-1.484000	-3.678000
H	1.032500	-0.379000	-2.821000
C	0.279500	-1.139000	-4.718000
H	0.657500	-0.255000	-5.269000
H	0.460500	-2.004000	-5.389000
C	-1.206500	-0.994000	-4.448000
H	-1.410500	-0.050000	-3.903000
H	-1.756500	-0.916000	-5.407000
C	-1.718500	-2.182000	-3.652000
H	-2.810500	-2.087000	-3.499000
H	-1.583500	-3.111000	-4.247000
H	-7.879500	2.175000	-2.806000