SUPPLEMENTARY INFORMATION

The role of non-covalent interactions in 4-hydroxybenzylamine macrocyclisation: computational and synthetic evidence

Andrés Gonzalez-Oñate, Jorge Alí-Torres, Rodolfo Quevedo

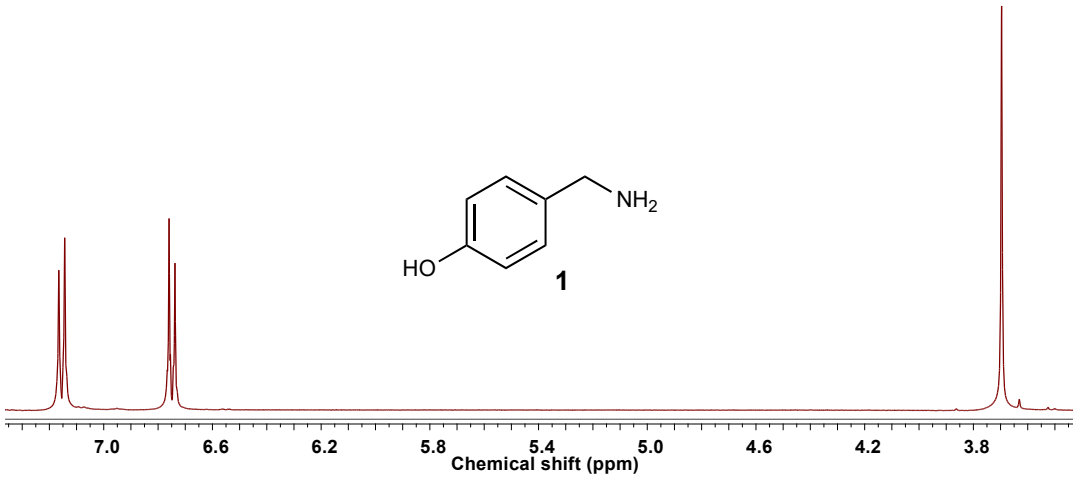
Universidad Nacional de Colombia, Sede Bogotá, Facultad de Ciencias, Departamento de Química, Carrera 30 No. 45-03, Bogotá, Colombia

4-hydroxybenzylamine 1 reaction with formaldehyde

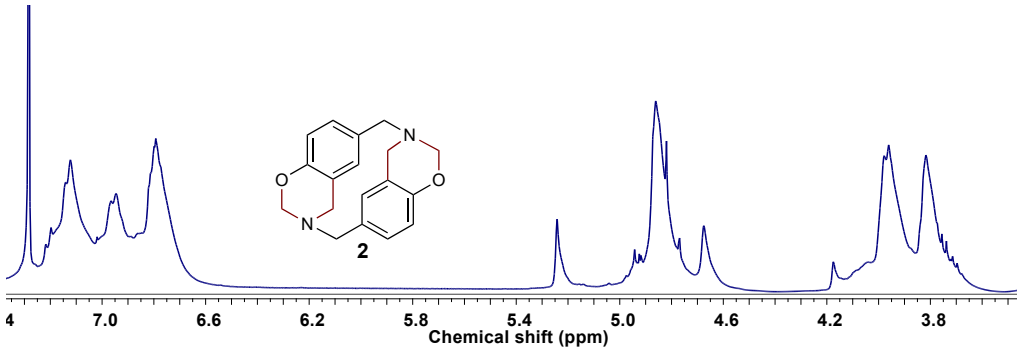
Formaldehyde (37%, 5 mL) was added to a 4-hydroxybenzylamine **1** solution (500 mg, 4 mmol) in 10 mL solvent (ethanol, dioxane, DMF and acetonitrile). The mixture was kept without stirring at room temperature for 24 h; distilled water (15 mL) was then added, and product was extracted with dichloromethane (3 x 5 mL). The organic phase was washed with water (3 x 5mL), dried with anhydrous sodium sulphate and concentrated. The resulting product was characterised by melting point, ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) and nuclear magnetic resonance (NMR) spectroscopy (^{1}H and ^{13}C).

Azacyclophane **2** (1^{3},1^{4},3^{3},3^{4}-tetrahydro-1^{2}H,3^{2}H–1,3(3,6)-*bis*(1,3-benzoxazine)cyclobutaphane): $C_{18}H_{18}N_2O_2$. Yellow Solid, m.p. 190-192 °C. ^{1}H-NMR ($CDCl^{3}$), δ/ppm: 7.27 – 6.67 (aromatic protons), 4.89 – 4.75 (benzoxazinic methylenes), 4.01 – 3.66 (benzylic methylenes). ^{13}C-NMR ($CDCl_3$), δ/ppm: 153.6, 130.5, 130.2, 128.6, 128.4, 120.0, 116.4, 81.9, 55.1, 49.8. ESI-MS (*m/z*): 271.4143 $[M+H-24]^{+}$ (Calc. 271.4146), 136,0756 $[M+2H-12]^{2+}$ (Calc. 136,0762). Yield: in ethanol: 52 %, in dioxane: 55 %, in DMF: 61 %, in acetonitrile: 59%.

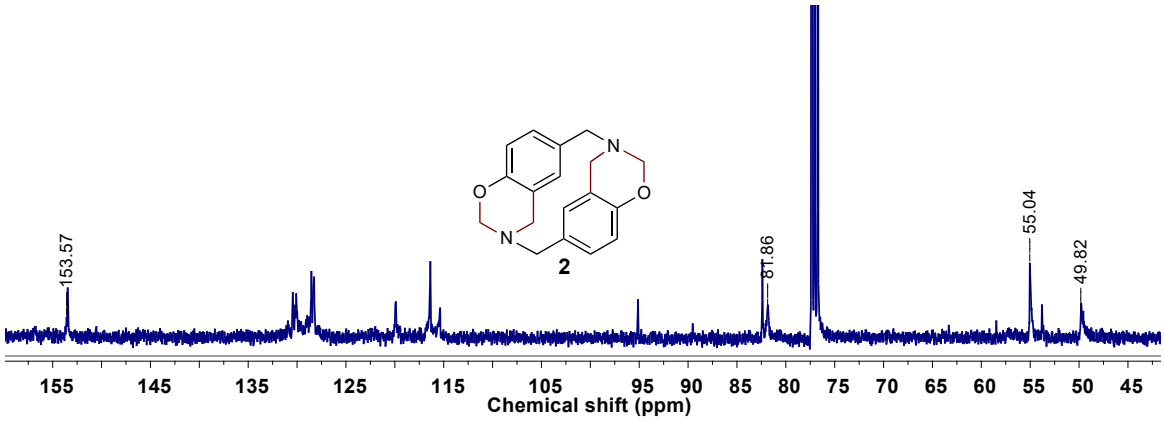
^{1}H-NMR spectrum of 4-hydroxybenzylamine 1.



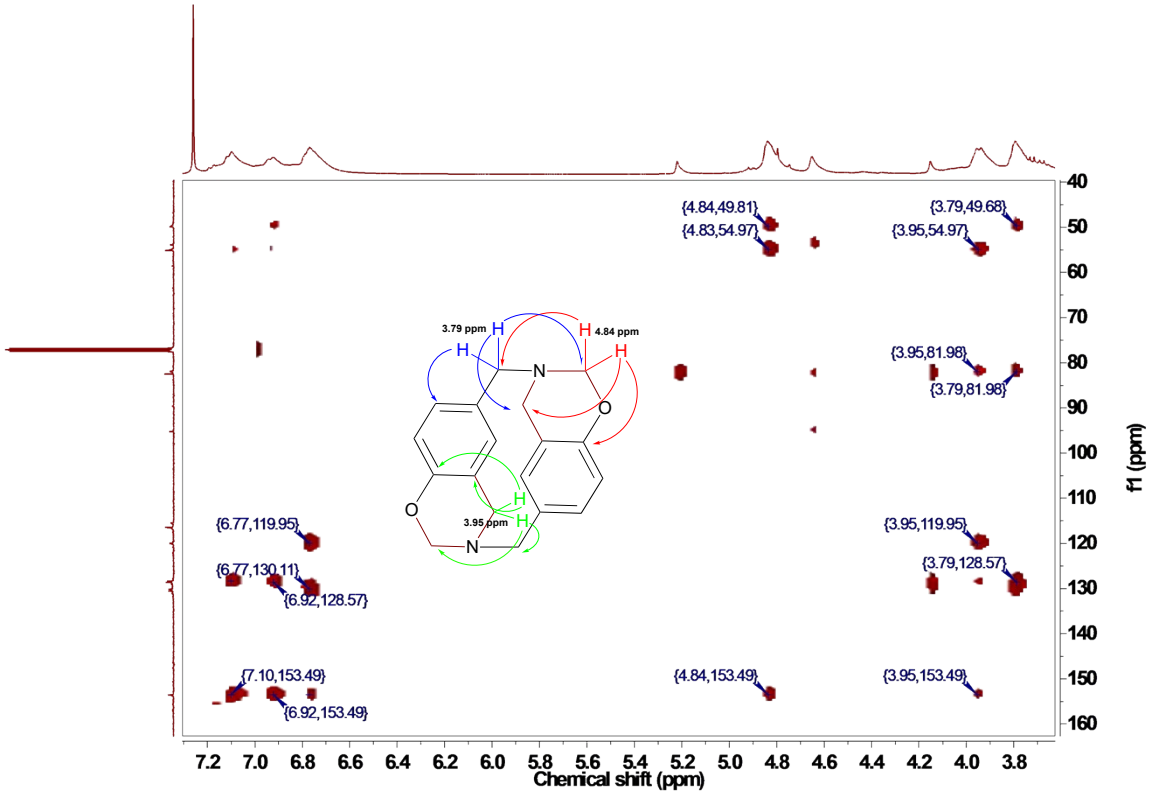
^{1}H-NMR spectrum of azacyclophane 2 synthesized in dioxane.



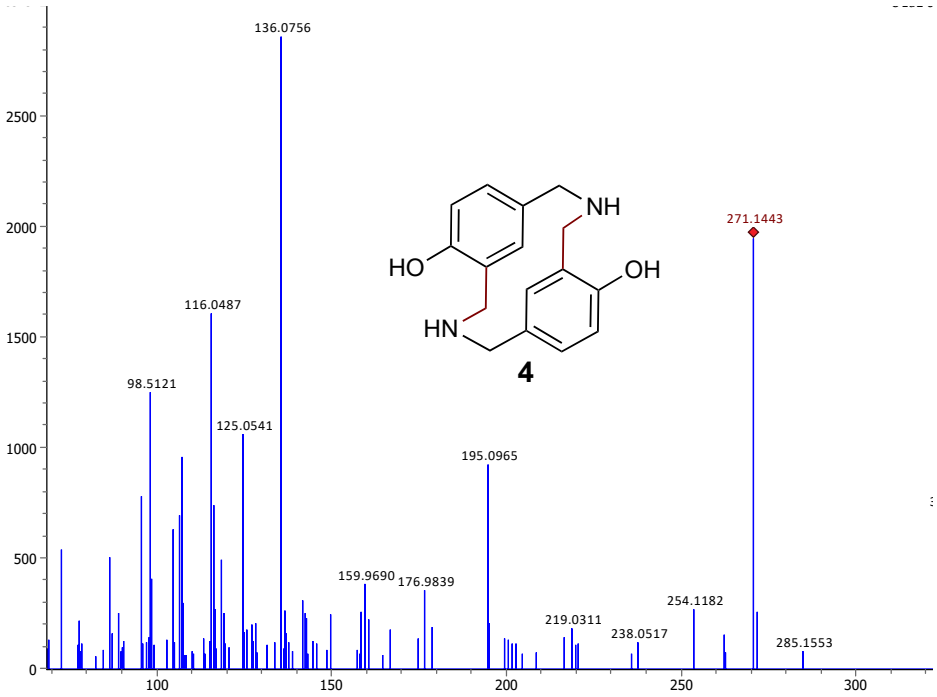
^{13}C-NMR spectrum of azacyclophane 2 synthesized in dioxane.



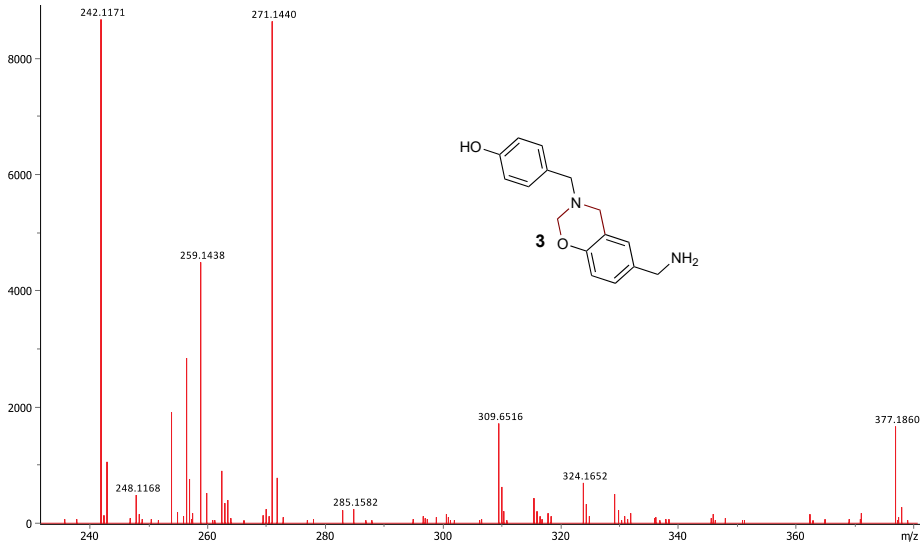
HMBC spectrum of azacyclophane 2 synthesized in dioxane.



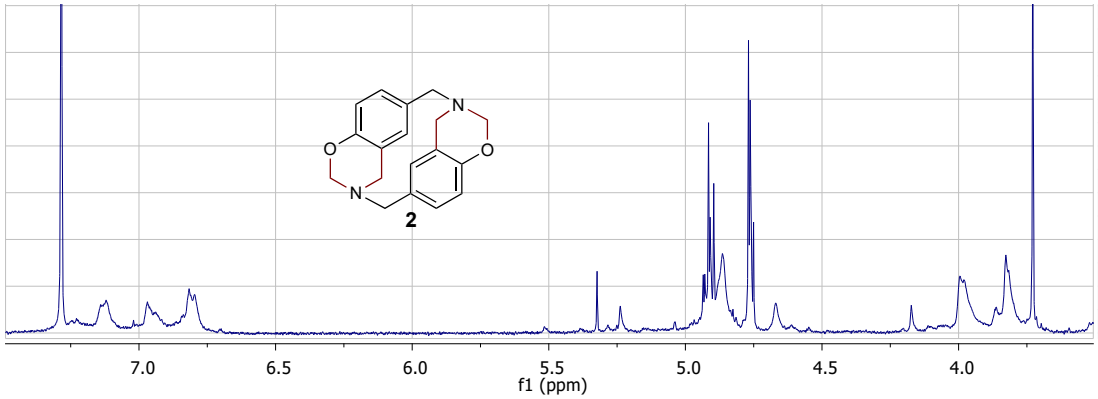
ESI-MS spectrum of azacyclophane 4 (derivative of azacyclophane 2 synthesized in dioxane).



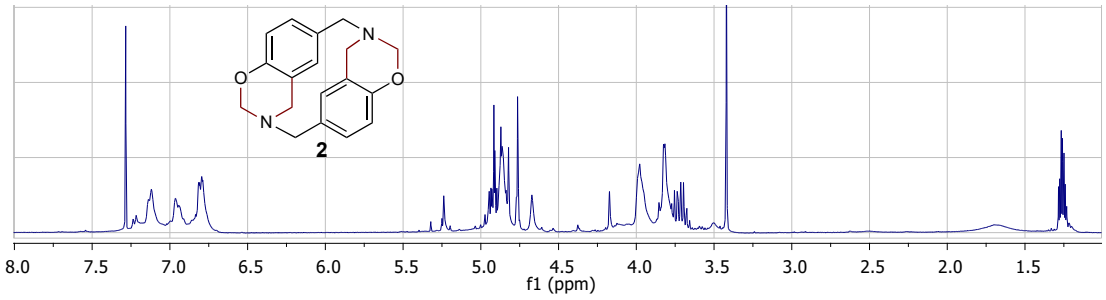
ESI-MS spectrum of linear dimer 3 (by-product of the synthesis in dioxane).



^{1}H-NMR spectrum of azacyclophane 2 synthesized in acetonitrile.



^{1}H-NMR spectrum of azacyclophane 2 synthesized in ethanol.



Geometrical Coordinates

Structure 1

18

Energy: -402.194559 Enthalpy: -402.005177 Free Energy: -402.047893

C	**-1.04543**	**-1.21793**	**0.12445**
C	**0.33138**	**-1.04415**	**0.23749**
C	**0.91198**	**0.23436**	**0.19128**
C	**0.06639**	**1.33477**	**0.02020**
C	**-1.31921**	**1.17749**	**-0.09188**
C	**-1.87573**	**-0.10249**	**-0.03852**
H	**-1.49264**	**-2.20622**	**0.16008**
H	**0.97712**	**-1.90937**	**0.35179**
H	**0.48875**	**2.33584**	**-0.02775**
H	**-1.95821**	**2.04786**	**-0.22671**
C	**2.40903**	**0.41507**	**0.34938**
H	**2.69451**	**0.22049**	**1.39200**
H	**2.65791**	**1.47056**	**0.14998**
O	**-3.22539**	**-0.33096**	**-0.14519**
H	**-3.69351**	**0.50755**	**-0.25015**
N	**3.15781**	**-0.53911**	**-0.48040**
H	**2.99709**	**-0.36338**	**-1.46913**
H	**4.15692**	**-0.46462**	**-0.31023**

Structure 1-GD3BJ

18

Energy: -402.194586 Enthalpy: -402.035145 Free Energy: -402.077840

C	**-1.03972**	**-1.21737**	**0.12665**
C	**0.33592**	**-1.04042**	**0.23970**

C	**0.91165**	**0.23897**	**0.19205**
C	**0.06581**	**1.33736**	**0.01899**
C	**-1.31859**	**1.17682**	**-0.09288**
C	**-1.87146**	**-0.10407**	**-0.03778**
H	**-1.48538**	**-2.20587**	**0.16307**
H	**0.98564**	**-1.90196**	**0.35451**
H	**0.48766**	**2.33804**	**-0.03091**
H	**-1.96002**	**2.04463**	**-0.22942**
C	**2.40640**	**0.42013**	**0.34576**
H	**2.69390**	**0.23657**	**1.38951**
H	**2.65626**	**1.47234**	**0.13238**
O	**-3.22016**	**-0.33480**	**-0.14461**
H	**-3.68802**	**0.50358**	**-0.25049**
N	**3.14568**	**-0.54636**	**-0.47652**
H	**2.96430**	**-0.38998**	**-1.46477**
H	**4.14707**	**-0.46302**	**-0.32632**

Structure 1a

36

Energy: -804.418836 Enthalpy: -804.020737 Free Energy: -804.084480

C	**1.39984**	**-1.49138**	**-1.16252**
C	**0.10913**	**-1.94186**	**-0.88638**
C	**-0.33607**	**-2.03617**	**0.44207**
C	**0.56602**	**-1.76492**	**1.47964**
C	**1.84968**	**-1.30673**	**1.18954**
C	**2.27866**	**-1.12742**	**-0.13291**
H	**2.51588**	**-1.04469**	**2.00795**
H	**1.71819**	**-1.40941**	**-2.20075**
H	**-0.56241**	**-2.21170**	**-1.69627**
H	**0.22577**	**-1.86475**	**2.50528**

O	**-1.61171**	**-2.38977**	**0.76011**
C	**3.60607**	**-0.47643**	**-0.44234**
N	**3.41518**	**0.93588**	**-0.88809**
H	**4.15581**	**-1.05772**	**-1.19768**
H	**4.22332**	**-0.44688**	**0.46036**
H	**2.98791**	**0.94104**	**-1.81300**
H	**4.32134**	**1.39119**	**-0.99126**
H	**-2.25786**	**-1.95039**	**0.14425**
H	**-0.22590**	**1.86549**	**2.50503**
H	**-2.51596**	**1.04520**	**2.00783**
C	**-0.56610**	**1.76534**	**1.47940**
C	**-1.84973**	**1.30703**	**1.18937**
O	**1.61163**	**2.39006**	**0.75981**
C	**0.33603**	**2.03632**	**0.44180**
N	**-3.41509**	**-0.93606**	**-0.88817**
H	**-2.98801**	**-0.94115**	**-1.81316**
H	**2.25785**	**1.95053**	**0.14415**
C	**-2.27864**	**1.12732**	**-0.13304**
H	**-4.32121**	**-1.39147**	**-0.99116**
C	**-3.60603**	**0.47622**	**-0.44234**
H	**-4.22316**	**0.44659**	**0.46044**
C	**-0.10910**	**1.94160**	**-0.88664**
C	**-1.39978**	**1.49101**	**-1.16271**
H	**0.56247**	**2.21123**	**-1.69658**
H	**-4.15593**	**1.05748**	**-1.19759**
H	**-1.71807**	**1.40873**	**-2.20094**

<u>Structure 1b</u>

36

Energy: -804.399745 Enthalpy: -804.009549 Free Energy: -804.079370

C	**2.09510**	**1.32435**	**1.24606**
C	**0.95466**	**2.12184**	**1.39153**
C	**0.19440**	**2.44521**	**0.26713**
C	**0.58299**	**1.99300**	**-0.99765**
C	**1.72035**	**1.20047**	**-1.12410**
C	**2.49267**	**0.84642**	**-0.00607**
H	**2.00786**	**0.82279**	**-2.10038**
H	**2.67300**	**1.06390**	**2.12986**
H	**0.65248**	**2.46890**	**2.37769**
H	**-0.02197**	**2.25078**	**-1.86085**
O	**-0.96737**	**3.18606**	**0.34605**
C	**3.71824**	**-0.03379**	**-0.15929**
N	**3.42379**	**-1.21994**	**-0.97339**
H	**4.10874**	**-0.26561**	**0.84639**
H	**4.51024**	**0.52405**	**-0.67727**
H	**2.74395**	**-1.82609**	**-0.51725**
H	**4.26562**	**-1.76334**	**-1.14185**
H	**-1.09300**	**3.49681**	**1.25234**
H	**0.01937**	**-2.25478**	**-1.86029**
H	**-2.01060**	**-0.82703**	**-2.10004**
C	**-0.58443**	**-1.99519**	**-0.99682**
C	**-1.72188**	**-1.20281**	**-1.12338**
O	**0.96758**	**-3.18573**	**0.34722**
C	**-0.19423**	**-2.44493**	**0.26836**
N	**-3.42416**	**1.21918**	**-0.97345**
H	**-2.74441**	**1.82573**	**-0.51772**
H	**1.09427**	**-3.49493**	**1.25389**
C	**-2.49276**	**-0.84652**	**-0.00504**
H	**-4.26610**	**1.76238**	**-1.14208**

C -3.71840 0.03353 -0.15850

H -4.51049 -0.52468 -0.67593

C -0.95300 -2.11926 1.39310

C -2.09361 -1.32201 1.24751

H -0.64956 -2.46438 2.37956

H -4.10865 0.26600 0.84713

H -2.67038 -1.05979 2.13152

Structure 1c

36

Energy: -804.408074 Enthalpy: -804.021209 Free Energy: -804.092231

C -3.37102 -0.22858 -1.12913

C -2.12190 -0.73262 -0.75881

C -1.79597 -0.87413 0.59883

C -2.74096 -0.50479 1.56803

C -3.98102 -0.00254 1.17943

C -4.32285 0.15205 -0.17399

H -4.70313 0.26931 1.94718

H -3.60728 -0.13417 -2.18748

H -1.40176 -1.01932 -1.52009

H -2.48798 -0.62771 2.61661

O -0.60159 -1.35944 1.02751

C -5.65443 0.75380 -0.58484

N -5.69887 2.22453 -0.69443

H -5.95870 0.34773 -1.55642

H -6.42997 0.46072 0.13219

H -5.45584 2.64903 0.19802

H -5.00211 2.54574 -1.36313

H -0.01277 -1.63919 0.27611

H 2.62002 2.15684 1.39777

H	**1.66870**	**-0.13654**	**1.34718**
C	**3.08348**	**1.37831**	**0.80073**
C	**2.56115**	**0.08869**	**0.76966**
O	**4.70101**	**2.96829**	**0.12735**
C	**4.22920**	**1.68377**	**0.05563**
N	**1.28966**	**-2.35029**	**-0.77092**
H	**1.40335**	**-1.93687**	**-1.69496**
H	**5.49286**	**3.06211**	**-0.41825**
C	**3.16223**	**-0.92089**	**-0.00279**
H	**0.99354**	**-3.31536**	**-0.91232**
C	**2.58720**	**-2.31851**	**-0.04495**
H	**2.39092**	**-2.68157**	**0.97028**
C	**4.84311**	**0.69466**	**-0.71735**
C	**4.30590**	**-0.59589**	**-0.74059**
H	**5.73546**	**0.92519**	**-1.29538**
H	**3.32376**	**-2.99705**	**-0.49718**
H	**4.79538**	**-1.35942**	**-1.34082**

Structure 1d

36

Energy: -804.400353 Enthalpy: -804.012948 Free Energy: -804.085862

C	**2.63163**	**1.05204**	**0.00621**
C	**1.35979**	**0.50632**	**-0.19581**
C	**1.19669**	**-0.88150**	**-0.19115**
C	**2.30405**	**-1.71322**	**0.01631**
C	**3.56254**	**-1.15320**	**0.22070**
C	**3.74903**	**0.23902**	**0.22278**
H	**4.42321**	**-1.79838**	**0.36842**
H	**2.74839**	**2.13338**	**-0.00768**
H	**0.50438**	**1.15577**	**-0.36535**

H	**2.16290**	**-2.78953**	**0.01163**
O	**-0.01977**	**-1.48331**	**-0.38918**
C	**5.11755**	**0.84043**	**0.47485**
N	**6.15487**	**0.17423**	**-0.32589**
H	**5.05778**	**1.92893**	**0.30924**
H	**5.39336**	**0.70120**	**1.52900**
H	**5.99472**	**0.32220**	**-1.31931**
H	**7.07719**	**0.53817**	**-0.10266**
H	**-0.71190**	**-0.81762**	**-0.52659**
H	**-2.82168**	**1.62844**	**-2.23043**
H	**-3.25119**	**-0.80141**	**-1.83055**
C	**-2.88514**	**1.23265**	**-1.22174**
C	**-3.12880**	**-0.12234**	**-0.99238**
O	**-2.48524**	**3.42512**	**-0.41874**
C	**-2.72553**	**2.10357**	**-0.13785**
N	**-2.87872**	**-2.97285**	**-0.43499**
H	**-1.86804**	**-2.98755**	**-0.31363**
H	**-2.41598**	**3.93043**	**0.40192**
C	**-3.21317**	**-0.63882**	**0.31199**
H	**-3.21850**	**-3.92651**	**-0.35730**
C	**-3.51958**	**-2.10639**	**0.55885**
H	**-4.60354**	**-2.26357**	**0.47320**
C	**-2.80240**	**1.60901**	**1.16778**
C	**-3.04012**	**0.24830**	**1.38134**
H	**-2.66568**	**2.27766**	**2.01515**
H	**-3.25299**	**-2.34587**	**1.60166**
H	**-3.08464**	**-0.12510**	**2.40155**

Structure 1e

36

Energy: -804.420779 Enthalpy: -804.098948 Free Energy: -804.161210

C	**1.26078**	**-1.45398**	**-1.16263**
C	**-0.04902**	**-1.80810**	**-0.84549**
C	**-0.46260**	**-1.84957**	**0.49484**
C	**0.47996**	**-1.60583**	**1.50291**
C	**1.78288**	**-1.24803**	**1.17182**
C	**2.18919**	**-1.13842**	**-0.16391**
H	**2.48427**	**-1.00357**	**1.96480**
H	**1.55686**	**-1.40856**	**-2.20918**
H	**-0.75832**	**-2.04254**	**-1.63262**
H	**0.15657**	**-1.64963**	**2.53722**
O	**-1.74225**	**-2.11978**	**0.85634**
C	**3.54780**	**-0.59239**	**-0.52104**
N	**3.43721**	**0.83126**	**-0.95097**
H	**4.02155**	**-1.20678**	**-1.30032**
H	**4.19928**	**-0.61281**	**0.35708**
H	**2.96343**	**0.87401**	**-1.85144**
H	**4.36394**	**1.23008**	**-1.09237**
H	**-2.37746**	**-1.76063**	**0.17724**
H	**-0.15628**	**1.64940**	**2.53698**
H	**-2.48403**	**1.00333**	**1.96475**
C	**-0.47979**	**1.60569**	**1.50269**
C	**-1.78274**	**1.24789**	**1.17172**
O	**1.74232**	**2.11985**	**0.85594**
C	**0.46265**	**1.84959**	**0.49454**
N	**-3.43737**	**-0.83135**	**-0.95054**
H	**-2.96353**	**-0.87436**	**-1.85097**
H	**2.37751**	**1.76068**	**0.17681**
C	**-2.18919**	**1.13843**	**-0.16397**

H	**-4.36414**	**-1.23009**	**-1.09193**
C	**-3.54784**	**0.59243**	**-0.52099**
H	**-4.19935**	**0.61314**	**0.35710**
C	**0.04893**	**1.80823**	**-0.84575**
C	**-1.26090**	**1.45411**	**-1.16277**
H	**0.75814**	**2.04278**	**-1.63292**
H	**-4.02150**	**1.20666**	**-1.30046**
H	**-1.55711**	**1.40879**	**-2.20929**

Structure 1f

36

Energy: -804.403349 Enthalpy: -804.081909 Free Energy: -804.148090

C	**1.97036**	**1.72149**	**0.83634**
C	**0.71896**	**2.30448**	**1.06028**
C	**-0.30036**	**2.12078**	**0.12638**
C	**-0.07447**	**1.36421**	**-1.02486**
C	**1.17686**	**0.79326**	**-1.23196**
C	**2.21969**	**0.96247**	**-0.30987**
H	**1.35294**	**0.18075**	**-2.10920**
H	**2.75946**	**1.86270**	**1.57134**
H	**0.53880**	**2.88411**	**1.96331**
H	**-0.88829**	**1.20158**	**-1.72254**
O	**-1.56575**	**2.64379**	**0.30286**
C	**3.58418**	**0.35331**	**-0.56279**
N	**3.47242**	**-0.97427**	**-1.17297**
H	**4.15118**	**0.36615**	**0.38438**
H	**4.14238**	**0.98944**	**-1.26319**
H	**3.02163**	**-1.62340**	**-0.53137**
H	**4.38781**	**-1.34133**	**-1.41418**
H	**-1.59328**	**3.16382**	**1.11619**

H	**0.39260**	**-2.85968**	**-1.16731**
H	**-1.91697**	**-2.14424**	**-1.76028**
C	**-0.20436**	**-2.27546**	**-0.47541**
C	**-1.49772**	**-1.87340**	**-0.79549**
O	**1.63856**	**-2.29534**	**1.01973**
C	**0.34726**	**-1.89536**	**0.75036**
N	**-3.52912**	**0.56185**	**-1.18697**
H	**-3.09252**	**1.34020**	**-0.69618**
H	**1.90920**	**-1.94474**	**1.87842**
C	**-2.26310**	**-1.10231**	**0.09047**
H	**-4.45100**	**0.86507**	**-1.49063**
C	**-3.63656**	**-0.60627**	**-0.29722**
H	**-4.17122**	**-1.39090**	**-0.84467**
C	**-0.39529**	**-1.13305**	**1.65036**
C	**-1.69396**	**-0.74689**	**1.31530**
H	**0.04100**	**-0.82627**	**2.59766**
H	**-4.21312**	**-0.40573**	**0.62129**
H	**-2.26499**	**-0.14182**	**2.01448**

Structure 1g

36

Energy: -804.408855 Enthalpy: -804.087082 Free Energy: -804.156299

C	**-2.76454**	**0.50242**	**-0.86417**
C	**-1.73729**	**1.14723**	**-0.17218**
C	**-1.36885**	**0.71086**	**1.11072**
C	**-2.05449**	**-0.37251**	**1.68118**
C	**-3.08015**	**-0.99930**	**0.97868**
C	**-3.45790**	**-0.57753**	**-0.30568**
H	**-3.59361**	**-1.84348**	**1.43434**
H	**-3.03007**	**0.85021**	**-1.86041**

H	**-1.22217**	**1.99053**	**-0.62141**
H	**-1.75705**	**-0.71312**	**2.66759**
O	**-0.37204**	**1.28428**	**1.82531**
C	**-4.61793**	**-1.22609**	**-1.03222**
N	**-5.95036**	**-0.66962**	**-0.73308**
H	**-4.46726**	**-1.14773**	**-2.11471**
H	**-4.65296**	**-2.29564**	**-0.79653**
H	**-6.14227**	**-0.75108**	**0.26308**
H	**-5.96236**	**0.32601**	**-0.94395**
H	**0.19939**	**1.86313**	**1.24955**
H	**1.67874**	**-2.43252**	**0.04560**
H	**0.62170**	**-0.25765**	**-0.49967**
C	**2.28572**	**-1.55076**	**-0.12818**
C	**1.70284**	**-0.32634**	**-0.43571**
O	**4.19989**	**-2.88204**	**0.26613**
C	**3.67825**	**-1.65274**	**-0.03831**
N	**1.38648**	**2.79850**	**0.30467**
H	**2.17177**	**2.89940**	**0.94588**
H	**5.16390**	**-2.83186**	**0.30290**
C	**2.48742**	**0.81551**	**-0.65988**
H	**1.03923**	**3.73711**	**0.11322**
C	**1.85036**	**2.15151**	**-0.94964**
H	**0.97202**	**2.01968**	**-1.58954**
C	**4.47813**	**-0.52865**	**-0.26128**
C	**3.87759**	**0.69383**	**-0.57042**
H	**5.56114**	**-0.60624**	**-0.20026**
H	**2.56183**	**2.78670**	**-1.49499**
H	**4.50735**	**1.56176**	**-0.75088**

Structure 1h

36

Energy: -804.407201 Enthalpy: -804.085597 Free Energy: -804.152525

C	**1.16568**	**-0.53086**	**-1.37398**
C	**-0.01248**	**-1.23007**	**-1.12506**
C	**-0.14762**	**-1.97678**	**0.05214**
C	**0.92857**	**-2.04693**	**0.94279**
C	**2.10432**	**-1.34084**	**0.68184**
C	**2.23756**	**-0.56067**	**-0.47369**
H	**2.93054**	**-1.38176**	**1.38433**
H	**1.24686**	**0.06150**	**-2.28226**
H	**-0.83824**	**-1.18217**	**-1.82757**
H	**0.81937**	**-2.63607**	**1.84804**
O	**-1.30014**	**-2.63452**	**0.36686**
C	**3.47138**	**0.27756**	**-0.74107**
N	**4.65508**	**-0.24123**	**-0.04600**
H	**3.60318**	**0.36330**	**-1.83267**
H	**3.29878**	**1.29763**	**-0.37324**
H	**4.91562**	**-1.15338**	**-0.41336**
H	**5.44815**	**0.37988**	**-0.17533**
H	**-2.08015**	**-2.17770**	**-0.03392**
H	**-0.10464**	**3.13044**	**-1.26982**
H	**-2.27021**	**2.08042**	**-1.87740**
C	**-0.58608**	**2.42624**	**-0.59990**
C	**-1.80123**	**1.83029**	**-0.92886**
O	**1.27570**	**2.63466**	**0.84959**
C	**0.05259**	**2.07215**	**0.59079**
N	**-3.70659**	**-1.23216**	**-0.14353**
H	**-3.93720**	**-1.34616**	**0.84144**
H	**1.67158**	**2.20494**	**1.61954**

C	**-2.40809**	**0.89109**	**-0.08551**
H	**-4.44315**	**-1.70886**	**-0.65839**
C	**-3.69158**	**0.20593**	**-0.50434**
H	**-3.78198**	**0.26958**	**-1.59278**
C	**-0.55416**	**1.16689**	**1.46324**
C	**-1.77609**	**0.58980**	**1.12456**
H	**-0.05539**	**0.87959**	**2.38453**
H	**-4.56215**	**0.73354**	**-0.08437**
H	**-2.20147**	**-0.14490**	**1.80067**