

An Examination of Factors Influencing Small Proton Chemical Shift Differences in Nitrogen-Substituted Monodeuterated Methyl Groups

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1/ Natural Bond Orbital Analysis of n-s* Delocalization Energies (Hyperconjugation) in *N*-Methyl-2-Methylpiperidine Rotamers

The geometry of the diequatorial structure of *N*-methyl-2-methylpiperidine was first optimized in *Gaussian 16*¹ using B3LYP/6-31G(d,p) theory. Route section: # opt b3lyp/6-31g(d,p) geom=connectivity. The coordinates for the optimized structure are provided in **Table S1**.

This structure was used as the starting point for a relaxed dihedral angle scan, at the same level of theory, for 360° rotation about the *N*-CH₃ bond in 10° increments, using C₄-N₁₉-C₂₀-H₂₁ as reference atoms for defining the dihedral angle (**Figure S1**). Route section: # opt=modredundant b3lyp/6-31g(d,p) geom=connectivity.

The structures generated in the relaxed dihedral angle scan were then assigned to a single molecule group in *GaussView 6* and subject to a batch process in which each structure was used for a single point B3LYP/3-31G(d,p) natural bond orbital (NBO) calculation. Route section: # b3lyp/6-31g(d,p) pop=(full,savenbos,nboread) geom=connectivity. The default threshold for NBO E(2) delocalization energies is 0.5 kcal/mol; this threshold was lowered to 0.001 kcal/mol by adding additional input in the form of a final line within the *Gaussian* input file: \$NBO E2PERT=0.001 \$END.

The E(2) values for each dihedral angle (q) are provided in **Table S2**.

Table S1. B3LYP/6-31G(d,p) Optimized Coordinates for *N*-Methyl-2-Methylpiperidine.

C	-1.94039900	0.72886500	0.24360400
C	-0.64324400	1.45497900	-0.12336500
C	0.61289700	0.67346800	0.30242900
C	-0.63537700	-1.41252100	0.13793900
C	-1.91032900	-0.69817900	-0.30953900
H	-0.60034200	1.60493400	-1.21035500
H	-0.61455600	2.44803400	0.34071700
H	-2.04207400	0.69263100	1.33748200
H	-2.81003500	1.27872900	-0.13487900

H	-0.59215900	-2.41320300	-0.30711000
H	-0.66505400	-1.55609100	1.23907800
H	-1.93451600	-0.67134100	-1.40601800
H	-2.78562600	-1.26844200	0.02342000
H	0.61356600	0.61073000	1.41278800
C	1.86881100	1.43894600	-0.12990700
H	1.79327900	2.48284600	0.19026000
H	2.78459000	1.03160700	0.30565600
H	1.96751900	1.42144900	-1.22061400
N	0.57212500	-0.68616400	-0.27038100
C	1.75682800	-1.47741900	0.04183900
H	2.65167500	-1.03429700	-0.39964800
H	1.93179900	-1.59500600	1.12962700
H	1.64192600	-2.47827400	-0.38573800

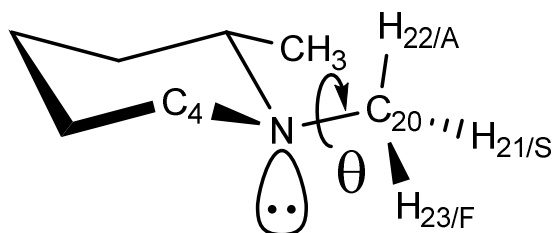


Figure S1. C₄-N₁₉-C₂₀-H₂₁ reference atoms used for defining dihedral angle q for B3LYP/6-31G(d,p) relaxed scan of methyl rotation in *N*-methyl-2-methylpiperidine.

Table S2. B3LYP/6-31G(d,p) N(lp)→CH s* delocalization energies (kcal/mol) in *N*-methyl-2-methylpiperidine.

$q/^\circ$ C ₄ -N-C ₂₀ -H ₂₁	E(2) N to CH ₂₁	E(2) N to CH ₂₂	E(2) N to CH ₂₃
-179.4	0.67	8.00	1.27
-169.4	0.22	7.56	1.89
-159.4	0.01	6.77	2.57
-149.4	0.11	5.65	3.26
-139.4	0.63	4.26	3.90
-129.4	1.62	2.75	4.37
-119.4	3.01	1.41	4.49
-109.4	4.54	0.50	4.20
-99.4	5.92	0.07	3.60
-89.4	7.00	0.02	2.87
-79.4	7.74	0.24	2.12
-69.4	8.09	0.64	1.41
-59.4	8.08	1.17	0.80
-49.4	7.67	1.80	0.31
-39.4	6.87	2.48	0.03
-29.4	5.66	3.21	0.07
-19.4	4.14	3.91	0.61

-9.4	2.59	4.41	1.77
0.6	1.31	4.48	3.29
10.6	0.48	4.15	4.80
20.6	0.08	3.54	6.08
30.6	0.01	2.83	7.07
40.6	0.22	2.09	7.75
50.6	0.64	1.40	8.10
60.6	1.20	0.80	8.10
70.6	1.85	0.33	7.77
80.6	2.55	0.04	7.03
90.6	3.25	0.06	5.88
100.6	3.91	0.57	4.32
110.6	4.39	1.74	2.61
120.6	4.50	3.38	1.21
130.6	4.17	5.01	0.37
140.6	3.54	6.35	0.03
150.6	2.79	7.31	0.05
160.6	2.01	7.90	0.31
170.6	1.29	8.13	0.73
180.6	0.67	8.00	1.27

2/ CH₂D Rotameric Population Analysis and Chemical Shifts in *N*-CH₂D-2-Methylpiperidine, *N*-CH₂D-3-Methylpiperidine and *trans*-1-CH₂D-2-CH₃-Cyclohexane

The structures of these compounds were optimized and harmonic frequencies calculated in *Gaussian 16* using wB97x/cc-PVTZ theory in a dichloromethane solvent continuum.² Route section: # opt=maxcycle=250 freq=noraman wb97x/cc-pvtz scrf=(solvent=dichloromethane,pcm) density=current geom=connectivity scf=(maxcycle=300,direct,tight). The coordinates for the optimized structures are provided in **Tables S3, S4 and S5**.

The wB97x/cc-PVTZ optimized geometries were then used for gauge-independent atomic orbital (GIAO) NMR shielding calculations in a methylene chloride solvent continuum using Hartree-Fock theory and the 6-311+G(2d,p) basis set.² Route section: # nmr=giao hf/6-311+g(2d,p) scrf=(solvent=dichloromethane,pcm) density=current geom=connectivity scf=(maxcycle=300,direct,tight).

The *Gaussian 16* freqchk utility program was used to obtain the isotopically perturbed thermochemistry (298.15 K, unscaled vibrational frequencies) from fully optimized geometries by means of deuterium replacement at positions 17, 18 and 19 in each of the structures (**Figure S2**).

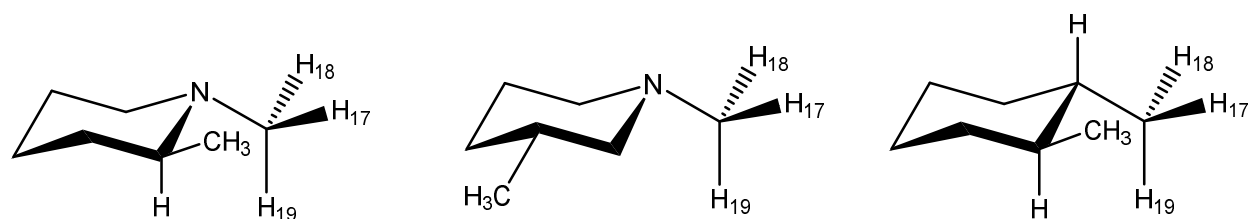


Figure S2. Methyl numbering scheme for (l-r): *N*-methyl-2-methylpiperidine, *N*-methyl-3-methylpiperidine and trans-1,2-dimethylcyclohexane.

The enthalpy and entropy values were extracted from each freqchk output and used to calculate a free energy for each CH₂D rotamer. The free energies were then used to compute the Boltzmann population of each rotamer.³

The proton shifts for each CH₂D proton were computed by taking the difference between the shielding values and that of tetramethylsilane (TMS) computed at the same level of theory (TMS = 32.26 ppm). Following this, the averaged chemical shift for the pro-*R* and pro-*S* protons were calculated from the proton shifts and the corresponding fractional populations using the following equations:

$$H_R = (P_{17} \times \text{Shift}_{19}) + (P_{18} \times \text{Shift}_{17}) + (P_{19} \times \text{Shift}_{18}) \text{ (S1)}$$

$$H_S = (P_{17} \times \text{Shift}_{18}) + (P_{18} \times \text{Shift}_{19}) + (P_{19} \times \text{Shift}_{17}) \text{ (S2)}$$

The Boltzmann population and chemical shift analyses for each compound are outlined in **Tables S6-S8**.

Table S3. wB97x/cc-PVTZ Optimized Coordinates for *N*-Methyl-2-Methylpiperidine.

C	-1.92565100	0.72349100	0.25223400
C	-0.63881100	1.44615800	-0.11863500
C	0.60817300	0.66432200	0.29090100
C	-0.62960500	-1.40270500	0.12453700
C	-1.90031500	-0.69154800	-0.30675200
H	-0.60281900	1.60264000	-1.20195700
H	-0.60343000	2.43167200	0.35073000
H	-2.01525300	0.67921200	1.34286100
H	-2.79410800	1.27324200	-0.11522300
H	-0.59059600	-2.40133200	-0.31449200
H	-0.64289000	-1.53600200	1.22316900
H	-1.93446000	-0.65781500	-1.39933200
H	-2.76821100	-1.26187600	0.02993000
H	0.60965700	0.58125900	1.39589800
C	1.85626700	1.42795900	-0.13125600
H	1.77915700	2.46565000	0.19530400
H	2.64417400	-1.03568000	-0.38050700
H	1.63219200	-2.47366900	-0.34172800
H	1.89209900	-1.54400400	1.14578100
H	2.76801200	1.01589400	0.29867600
H	1.95238000	1.41764900	-1.21926600
N	0.57009000	-0.68238200	-0.28657800
C	1.74385400	-1.46437000	0.05500600

Table S4. wB97x/cc-PVTZ Optimized Coordinates for *N*-Methyl-3-Methylpiperidine.

C	1.23192600	1.13342400	0.18714700
C	1.25261700	-0.29562000	-0.34799000
C	-0.01495400	-1.02353400	0.08435400
C	-1.26962700	1.01476000	0.23598800
C	-0.06499600	1.83887500	-0.19061000
H	1.24415700	-0.24988100	-1.44239800
H	1.32261800	1.10036000	1.27972500
H	2.09672600	1.68786900	-0.18498500
H	-2.19399400	1.49383700	-0.09320300
H	-1.30645100	0.96572800	1.34138800
H	-0.10272700	1.98465800	-1.27368400
H	-0.11688300	2.82616800	0.27227400
H	0.00402400	-1.14824300	1.18574100
N	-1.22025800	-0.32416000	-0.33021800
C	-2.40334200	-1.07974200	0.02295200
C	2.49381600	-1.05176200	0.10297200
H	-2.37067300	-2.06517700	-0.44356900
H	-3.29623200	-0.56279300	-0.33105500
H	-2.50083000	-1.22140300	1.11297700
H	2.51332200	-2.06505600	-0.30289600
H	3.40194400	-0.54163700	-0.22264900
H	2.52671900	-1.12642200	1.19307000
H	-0.03256500	-2.02729600	-0.34808300

Table S5. wB97x/cc-PVTZ Optimized Coordinates for *trans*-1,2-dimethylcyclohexane.

C	-1.93315700	-0.70441300	-0.29104200
C	-0.66797700	-1.45603600	0.10572100
C	0.60982500	-0.71204000	-0.28903900
C	-0.66797300	1.45603900	-0.10571500
C	-1.93315700	0.70441600	0.29103600
H	-0.66257300	-1.60671200	1.19250100
H	-0.66192800	-2.45195000	-0.34538800
H	-1.98778500	-0.64228000	-1.38349700
H	-2.81826300	-1.25407100	0.03685500
H	-0.66192700	2.45194800	0.34540400
H	-0.66256300	1.60672600	-1.19249300
H	-1.98779300	0.64228000	1.38349100
H	-2.81825800	1.25407700	-0.03686600
H	0.61601100	-0.61669200	-1.38383900
C	1.83636000	-1.51690400	0.12749700
H	1.76927500	-2.54131400	-0.24412300
H	2.76287300	1.08791300	0.25415100
H	1.76923900	2.54134000	0.24402400
H	1.91208700	1.56373000	-1.21775200
H	2.76287700	-1.08786200	-0.25406800
H	1.91202400	-1.56383200	1.21774800

C	1.83636600	1.51689800	-0.12750100
C	0.60982800	0.71204100	0.28904400
H	0.61601900	0.61669400	1.38384400

Table S6. Boltzmann Population and pro-*R* and pro-*S* Chemical Shift Analysis for *N*-methyl-2-methylpiperidine.

N-methyl-2-methylpiperidine			opt/freq:	wb97x cc-pvtz			
		D=17	D=19	D=18			
	ZPVE	133.8128	133.9029	133.8267		T = 298.15K	
	H	139.0180	139.1070	139.0320			
	S	86.9470	86.9800	86.9530			
	G	113.0948	113.17391	113.1069631			
	delG	0	0.079161	0.0122111			
	Nj	1	0.8749322	0.979600916			
	N	2.854533					
	populations	0.35032	0.3065062	0.343173773			
					NMR: hf/6-311+G(2d,p)		
		H=17	H=19	H=18		TMS	
shielding		29.7179	30.6624	30.2695		32.26	ppm
shift		2.5421	1.5976	1.9905			
H _R	2.0421539	ppm					
H _S	2.0247359	ppm					
H _R -H _S =	0.0174181	ppm					

Table S7. Boltzmann Population and pro-*R* and pro-*S* Chemical Shift Analysis for *N*-methyl-3-methylpiperidine.

N-methyl-3-methylpiperidine			opt/freq:	wb97x cc-pvtz			
		D=17	D=19	D=18			
	ZPVE	133.6747	133.7332	133.6736		T = 298.15K	
	H	138.9350	138.9930	138.9340			
	S	87.3280	87.3400	87.3280			
	G	112.8982	112.95258	112.8971568			
	delG	0	0.0544222	-0.001			
	Nj	1	0.912238	1.001689235			
	N	2.913927					
	populations	0.343179	0.3130614	0.343759178			
					NMR: hf/6-311+G(2d,p)		
		H=17	H=19	H=18		TMS	
shielding		30.1479	30.5685	30.1342		32.26	
shift		2.1121	1.6915	2.1258			
H _R	1.9720477	ppm					
H _S	1.9722164	ppm					
H _R -H _S =	-0.0001688	ppm					

Table S8. Boltzmann Population and pro-*R* and pro-*S* Chemical Shift Analysis for trans-1,2-dimethylcyclohexane.

trans-1,2-dimethylcyclohexane			opt/freq:	wb97x cc-pvtz			
		D=17	D=19	D=18			
	ZPVE	140.9333	140.9642	140.9455		T = 298.15K	
	H	146.3180	146.3480	146.3300			
	S	88.1740	88.1970	88.1790			
	G	120.0289	120.05206	120.0394312			
	delG	0	0.0231426	0.01050925			
	Nj	1	0.9616928	0.982418766			
	N	2.944112					
	populations	0.339661	0.3266496	0.333689383			
					NMR:	hf/6-311+G(2d,p)	
		H=17	H=19	H=18		TMS	
shielding		31.0088	31.7759	31.4957		32.26	
shift		1.2512	0.4841	0.7643			
H _R	0.8316003	ppm					
H _S	0.8298459	ppm					
H _R -H _S =	0.0017544	ppm					

3/ CH₂D Rotameric Population Analysis and NBO Analysis in 1-CH₂D-2-methylphosphinane

The structure was optimized and harmonic frequencies calculated in *Gaussian 16* using B3LYP/6-31(d,p) theory.² Route section: # opt freq b3lyp/6-31g(d,p) geom=connectivity. The coordinates for the optimized structure are provided in **Table S9**.

The *Gaussian 16* freqchk utility program was used to obtain the isotopically perturbed thermochemistry (298.15 K, unscaled vibrational frequencies) from fully optimized geometries by means of deuterium replacement at positions 21, 22 and 23 (**Figure S3**).

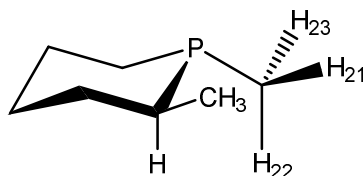


Figure S3. Methyl numbering scheme for 1,2-dimethylphosphinane.

The Boltzmann population analysis is outlined in **Table S10**.

A B3LYP/3-31G(d,p) NBO calculation was performed on the optimized structure. Route section: # b3lyp/6-31g(d,p) pop=(full,savenbos,nboread) geom=connectivity. The default threshold for NBO E(2) delocalization energies is 0.5 kcal/mol; this threshold was lowered to 0.001 kcal/mol by adding additional input in the form of a final line within the *Gaussian* input file: \$NBO E2PERT=0.001 \$END.

The E(2) values for the P(lp) / 1-methyl C-H bond interactions are provided in **Table S11**.

Table S9. B3LYP/6-31G(d,p) Optimized Coordinates for 1,2-dimethylphosphinane.

C	-2.11537200	0.52200000	0.39401600
C	-1.00072000	1.47158500	-0.07361500
C	0.42225900	0.99596200	0.28171800
C	-0.69369700	-1.58938800	0.12273300
C	-2.02056900	-0.88778400	-0.21051100
H	-1.07340900	1.61213700	-1.16174700
H	-1.16009800	2.46316300	0.37214400
H	-2.08391600	0.44466000	1.49027800
H	-3.08995800	0.95917900	0.14481600
H	-0.68048400	-2.60277400	-0.29440700
H	-0.58579400	-1.68564600	1.21225700
H	-2.13698400	-0.82359600	-1.30088200
H	-2.85726500	-1.49731700	0.15363000
H	0.46242700	0.81774600	1.36736000
C	1.47573800	2.04891100	-0.08579200
H	1.27095100	2.99749400	0.42514700
H	2.48577700	1.73474600	0.19722000
H	1.47826400	2.24402600	-1.16388100
P	0.76158600	-0.64251300	-0.58857200
C	2.14024800	-1.32731400	0.46781300
H	3.06922100	-0.78676900	0.26484300
H	1.92306700	-1.26700000	1.54032800
H	2.30709700	-2.37618300	0.20330800

Table S10. Boltzmann Population Analysis for 1,2-dimethylphosphinane.

1,2- dimethylphosphinane	opt/freq:		b3lyp/6- 31g(d,p)	T = 298.15K
	D=21	D=22	D=23	
ZPVE	128.6807	128.6893	128.6874	
H	134.7620	134.7720	134.7690	
S	93.7850	93.7790	93.7900	
G	106.8	106.81179	106.8055115	
delG	0	0.0117889	0.00550925	
Nj	1	0.9802992	0.99074453	
N	2.971044			
populations	0.336582	0.3299511	0.333466826	

Table S11. B3LYP/6-31G(d,p) P(lp)→CH σ^* delocalization energies (kcal/mol) in 1,2-dimethylphosphinane.

E(2) P to CH ₂₁	E(2) P to CH ₂₂	E(2) P to CH ₂₃
0.01	3.09	0.00

4/ Conformational Energies and ¹H NMR Chemical Shifts in Methyl 1-Methylpiperidine Carboxylate Rotamers

The GS1 geometry of the diequatorial structure of methyl 1-methylpiperidine carboxylate was first optimized in *Gaussian 16* using B3LYP/6-31G(d) theory. Route section: # opt b3lyp/6-31g(d) geom=connectivity. The coordinates for the optimized structure are provided in **Table S12**.

This structure was used as the starting point for a relaxed dihedral angle scan, at the same level of theory, for 360° rotation about the C₃-C₂₀ bond in 10° increments, using N₁₅-C₃-C₂₀-O₂₁ as reference atoms for defining the dihedral angle (**Figure S4**). Route section: # opt=modredundant b3lyp/6-31g(d) geom=connectivity.

The relative energies for each dihedral angle (q) are provided in **Table S13**.

The scan revealed one minimum energy structure in addition to GS1. This structure (GS2) was then fully optimized in *Gaussian 16* using B3LYP/6-31G(d) theory. Route section: # opt b3lyp/6-31g(d) geom=connectivity. The coordinates for the optimized structure are provided in **Table S14**.

The B3LYP/6-31G(d) optimized geometries of GS1 and GS2 were then used for GIAO NMR shielding calculations in a chloroform solvent continuum using the WP04 density functional and the cc-PVTZ basis set. Route section: # nmr=giao blyp/cc-pvdz scrf=(solvent=chloroform) geom=connectivity iop(3/76=1000001189,3/77=0961409999,3/78=0000109999).

This procedure^{4,5} directly reveals ¹H chemical shifts, which are obtained by scaling the shielding values m according to the equation $\delta^1\text{H} = (31.8444 - m)/1.0205$.

The ¹H NMR shielding values and chemical shifts for the N-CH₃ hydrogen atoms are compiled in **Table S15**.

Table S12. B3LYP/6-31G(d) Optimized Coordinates for Methyl 1-Methylpiperidine Carboxylate (GS1 Conformation).

C	-1.98612700	-1.73545500	-0.13768100
C	-0.52932000	-1.46159300	0.24656100
C	-0.04851800	-0.09367500	-0.29716900
C	-2.31688300	0.75071000	-0.25861300
C	-2.86771000	-0.56198500	0.29896400
H	-0.43091300	-1.44327000	1.33923200
H	0.13317600	-2.24560800	-0.13646400
H	-2.06008400	-1.86533000	-1.22720000
H	-2.32580700	-2.67392600	0.31743400
H	-2.91408600	1.59435100	0.10650200
H	-2.41436000	0.74701100	-1.36578600
H	-2.88958500	-0.50209100	1.39461900
H	-3.90081600	-0.69899000	-0.04367900
H	-0.00878200	-0.15519900	-1.40326700
N	-0.92826200	0.98434200	0.14990900
C	-0.48058200	2.29849900	-0.30141800
H	0.51139800	2.51556800	0.09915800
H	-0.44954800	2.38887300	-1.40562100
H	-1.16970500	3.05999500	0.07834000
C	1.38497900	0.10070700	0.19545900

O	1.73236100	0.67081300	1.20484900
O	2.24734300	-0.52780400	-0.63979700
C	3.62404400	-0.50425200	-0.23020400
H	3.74486000	-0.98455200	0.74462300
H	4.16802000	-1.05391000	-0.99903300
H	3.98713000	0.52486500	-0.16402900

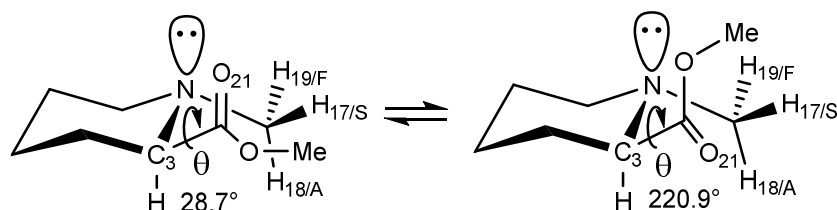


Figure S4. N₁₅-C₃-C₂₀-O₂₁ reference atoms used for defining dihedral angle q for B3LYP/6-31G(d) relaxed scan of ester rotation in methyl 1-methylpiperidine carboxylate.

Table S13. B3LYP/6-31G(d) conformational energies (kcal/mol) for ester rotation in methyl 1-methylpiperidine carboxylate.

$q/^{\circ}$ N ₁₃ -C ₃ -C ₂₀ -O ₂₁	Energy (relative)
28.706	-5E-07
38.706	0.0703
48.706	0.2189
58.706	0.3768
68.706	0.5489
78.706	0.8054
88.706	1.2037
98.706	1.7531
108.71	2.4259
118.71	3.1766
128.71	3.93
138.71	4.524
148.71	4.6231
158.71	4.0727
168.71	3.1437
178.71	2.1469
188.71	1.3049
198.71	0.7114
208.71	0.3716
218.71	0.244
228.71	0.2846
238.71	0.4611
248.71	0.7387
258.71	1.0962

268.71	1.515
278.71	1.9929
288.71	2.529
298.71	3.0901
308.71	3.5434
318.71	3.6522
328.71	3.2947
338.71	2.5886
348.71	1.7553
358.71	0.9926
368.71	0.4236
378.71	0.0972
388.71	-2E-06

Table S14. B3LYP/6-31G(d) Optimized Coordinates for Methyl 1-Methylpiperidine Carboxylate (GS2 Conformation).

C	2.22692700	-1.50822700	0.06409100
C	0.69632000	-1.50134600	0.00585200
C	0.11985300	-0.17499300	0.55293200
C	2.14714600	0.99962100	-0.06855300
C	2.77987600	-0.26780500	-0.64446500
H	0.36298100	-1.61492000	-1.03263200
H	0.27732000	-2.33280900	0.58471700
H	2.55471900	-1.50845100	1.11368800
H	2.61773100	-2.42689900	-0.39020400
H	2.49753600	1.88018800	-0.61988000
H	2.47932500	1.12854200	0.98380900
H	2.55469600	-0.32230300	-1.71733000
H	3.87037600	-0.21030100	-0.54007600
H	0.33122500	-0.12039100	1.63841400
N	0.68363900	0.97315700	-0.16124500
C	0.12139800	2.23761600	0.30037600
H	-0.95944200	2.25434100	0.13375600
H	0.31250400	2.43369500	1.37345300
H	0.55960300	3.05845100	-0.27715600
C	-1.40322100	-0.25300300	0.45588900
O	-2.12268900	-0.55312500	1.38472900
O	-1.85652600	-0.02882200	-0.79545500
C	-3.27706000	-0.16393100	-0.96357200
H	-3.81053900	0.53788300	-0.31680500
H	-3.46903300	0.05949700	-2.01342600
H	-3.59818000	-1.18064500	-0.72110700

Table S15. WP04/cc-PVDZ (PCM = chloroform) ¹H NMR shielding values and calculated chemical shifts in the GS1 and GS2 conformers of methyl 1-methylpiperidine carboxylate.

conformer	H label	shielding (ppm)	calculated shift (ppm)
GS1	H-17/S	29.1881	2.59
GS1	H-18/A	30.069	1.73
GS1	H-19/F	29.7928	2.00
GS2	H-17/S	29.5454	2.24
GS2	H-18/A	29.8961	1.90
GS2	H-19/F	29.716	2.08

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