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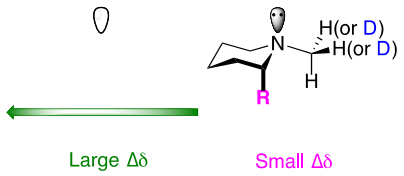
On the Origins of Small Proton Chemical Shift Differences in Monodeuterated Methyl Groups

O. Maduka Ogba,[†] Stuart J. Elliott,[‡] David A. Kolin,[†] Lynda J. Brown,[‡] Sebastian Cevallos,[†] Stuart Sawyer,[‡] Malcolm H. Levitt,[‡] Daniel J. O'Leary[†,*]

[†]Department of Chemistry, Pomona College, 645 North College Avenue, Claremont, California 91711.

[‡]School of Chemistry, University of Southampton, Southampton SO17 1BJ, United Kingdom

Supporting Information Placeholder

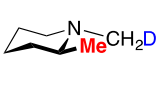


ABSTRACT: We have recently shown that the small proton chemical shift difference in 2-methyl-1-(methyl-*d*)piperidine supports a long-lived nuclear spin state. To identify additional candidate molecules with CH_2D groups exhibiting accessible long-lived states, and to investigate the factors governing the magnitude of the shift differences, we report a computational and experimental investigation of methyl rotational dynamics and proton chemical shifts in a variety of 2-substituted 1-(methyl-*d*)piperidines. The polarity and size of the 2-substituent affect the 1,2-stereoisomeric relationship and consequently the strength of the rotational asymmetry within the CH_2D group. Non-polar and large 2-substituents prefer the equatorial position, and relatively large shift differences (i.e., > 13 ppb) are observed. Polar and small substituents, however, increasingly prefer the axial position, and medium to small shift differences (i.e., 0 to 9 ppb) are observed. In addition, diastereotopic CH_2D proton chemical shift difference for tricarbonyl(1-chloro-2-deuteriomethylbenzene) chromium(0) was computed, showing that reasonable predictions of these small shift differences can be extended to more complex, organometallic species.

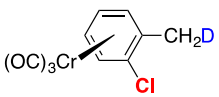
Introduction

The discovery of long-lived nuclear spin states (LLS)[1–3] in a variety of molecular systems has attracted significant interest. LLS lifetimes often surpass the characteristic relaxation time of ordinary magnetization (T_1) by an order of magnitude.[2] LLS are particularly promising in combination with the large sensitivity improvements afforded by NMR hyperpolarization.[3,4a] Applications benefiting from substantial NMR signal enhancements include: imaging and monitoring of cancer in human patients,[4a] targeting molecules relevant to neuroscience,[4b] protein unfolding mechanisms,[4c] and measuring slow diffusion coefficients of large biomolecules.[4d]

The generation of long-lived states typically requires combining radiofrequency pulse sequences with chemically inequivalent and scalar coupled nuclei. The extension of these techniques to methyl groups requires CH_2D groups consisting of diastereotopic protons with different chemical shifts. For technical reasons that relate to LLS pulse sequences,[2d,f] very small chemical shift differences (<20 ppb) were viewed as particularly ideal. We have recently shown that a LLS is supported in the monodeuterated methyl groups of two molecules: 2-methyl-1-(methyl-*d*)piperidine[5] and tricarbonyl(1-chloro-deuteriomethylbenzene)chromium(0)[6]. Both LLS were accessed via small proton chemical shift differences (ca. 13 and 8 ppb, respectively) between the diastereotopic protons of their corresponding CH_2D groups (**Figure 1**).



2-methyl-1-(methyl-*d*)piperidine
T_S/T_1 = 3.1
Δδ = 13.5 ± 0.4 ppb



tricarbonyl(1-chloro-2-deuteriomethylbenzene) chromium(0)
T_S/T_1 = 11.1 ± 0.8
Δδ = 8.0 ± 0.4 ppb

Figure 1. Ratios of T_S, the singlet order relaxation time constant, and T_1, the longitudinal relaxation time constant, and the small chemical shift differences (Δδ) for the diastereotopic CH_2D protons of 2-methyl-1-(methyl-*d*)piperidine and tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0). [5,6]

To the best of our knowledge, there are only three reported cases shown to induce chemical shifts between diastereotopic protons of the CH_2D group,[7–10] and little is known about the factors governing the magnitude of these shift differences. In the case of 2-methyl-1-(methyl-*d*)piperidine, previous measurements and predictions by Anet and Kopelevich,[7] and computations by us,[8,9] have shown that due to hyperconjugation effects between the lone pair of the piperidine nitrogen and an *anti*-methyl C-H(D) bond, and the local chiral environment around the CH_2D group, an asymmetric population distribution of the three CH_2D rotamers is achieved. This results in a small secondary equilibrium isotope effect and corresponds to a shift difference between the CH_2D protons, observed using ^1H NMR spectroscopy.

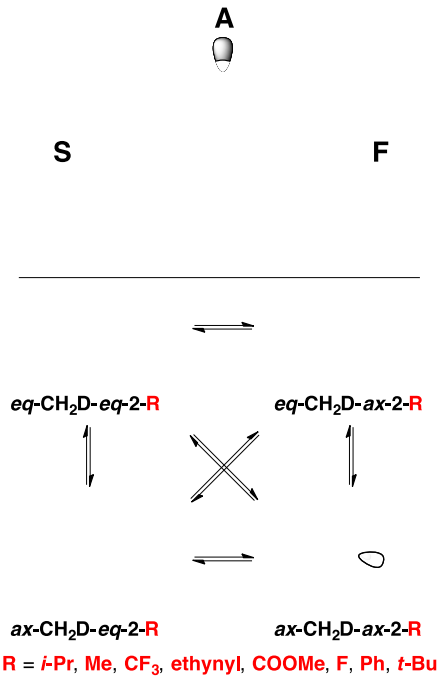
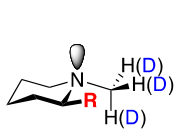
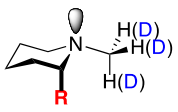
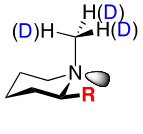
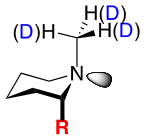


Figure 2. The three CH_2D rotamers, labeled as deuterium positioned *anti* to N lone-pair (**A**), in *steric* proximity to R group (**S**), and relatively *free* from steric hindrance of R group (**F**) (Top). The four stereoisomers of each substituted piperidine (Middle). The eight 2-substituted 1-(methyl-*d*)piperidines computed in this study (Bottom).

Encouraged by these results, we set out to explore a variety of 2-substituted 1-(methyl-*d*)piperidines (**Figure 2**). Our goal was to understand how the steric and electronic nature of the 2-substituent perturbs the EIE and proton shift differences in this family of compounds. Through joint computational and experimental efforts, we discovered that, in general, the magnitude of chemical shift difference between CH_2D protons is affected by the preferred stereoisomeric relationship between the CH_2D group and the 2-substituent on the piperidine ring. Non-polar and large 2-substituents prefer the equatorial position, and relatively large shift differences (i.e., > 13 ppb) are observed. Polar and small substituents, however, increasingly prefer the axial position, and medium to small shift differences (i.e., 0 to 9 ppb) are observed.

We computed the weighted average of shift differences for all populated states in each piperidine species to accurately predict proton chemical shift differences of the kind described above.[11] To accomplish this, a gas-phase conformational search was performed using the Merck Molecular Force Field (MMFFs)[12] as implemented in Schrödinger MacroModel suite.[13] Quantum mechanical computations in Gaussian 09[14] to obtain refined structures and energies for each conformer were performed at the ωB97X[15]/cc-pVTZ[16] level of theory, including the polarizable continuum model (PCM)[17] for dichloromethane. All stationary points were verified as minima by a vibrational frequency analysis. For each optimized structure, the thermochemistry of the CH_2D rotamers were obtained at the same level of theory. NMR isotropic shielding constants, and thus chemical shifts, for each structure were computed at the HF[18]/6-311+G(2d,p)[19,20] level of theory including PCM for dichloromethane.[21] The averaged chemical shift differences were computed as the weighted sum of the chemical shift difference for each rotamer in each conformer and stereoisomer.[22,23]

Table 1. Mole fractions (χ) of CH_2D rotamers across stereoisomers, and corresponding computational (comp) and experimental (exp) chemical shift differences (Δδ) between pro-chiral CH_2D protons (i.e., H_R and H_S, see **Figure 2**) in eight 2-substituted 1-(methyl-*d*)piperidine compounds. Significant fractional populations of stereosiomers ($\chi_{S+F+A} > 0.1$) reported in **bold**.[24]

Entry	R	χ_S	χ_F	χ_A	χ_S	χ_F	χ_A	χ_S	χ_F	χ_A	χ_S	χ_F	χ_A	$\Delta\delta_{comp}$	$\Delta\delta_{exp}{}^a$
														Averaged Chemical Shift Differences (Δδ, H_R-H_S) in ppb	

I	*i*-Pr	**0.329**	**0.325**	**0.283**	0.000	0.000	0.000	0.012	0.011	0.011	0.005	0.005	0.005	22.9	–[b]
II	Me	**0.333**	**0.321**	**0.288**	0.017	0.017	0.016	0.002	0.002	0.002	0.000	0.000	0.000	13.2	13.5[c]
III	CF_3	**0.202**	**0.192**	**0.174**	**0.117**	**0.119**	**0.114**	0.017	0.016	0.015	0.011	0.011	0.010	6.9	7.1
IV	Ethynyl	**0.083**	**0.083**	**0.075**	**0.255**	**0.260**	**0.240**	0.001	0.001	0.001	0.000	0.000	0.000	4.7	6.6
V	COOMe[d]	**0.279**	**0.272**	**0.249**	**0.066**	**0.066**	**0.063**	0.001	0.001	0.001	0.000	0.000	0.000	2.6	2.2
VI	F	0.001	0.001	0.001	**0.336**	**0.338**	**0.323**	0.000	0.000	0.000	0.000	0.000	0.000	1.3	–[b]
VII	Ph	0.000	0.000	0.000	**0.228**	**0.229**	**0.216**	0.000	0.000	0.000	**0.110**	**0.110**	**0.107**	0.3	<1
VIII	*t*-Bu	0.021	0.020	0.018	0.000	0.000	0.000	**0.297**	**0.290**	**0.274**	0.027	0.027	0.025	–10.2	–[b]

[a] All experimental ^{1}H spectra can be found in the Supporting Information. Experimentally determined chemical shifts reported to ± 0.4 ppb precision. [b] Not prepared. [c] $\Delta\delta_{exp}$ for 2-ethyl-1-(methyl-*d*)piperidine was also experimentally determined to be 13.7 ± 0.4 ppb. [d] Multiple conformers were computed for each stereoisomer. Reported mole fractions are from the sum of all computed conformers. $\Delta\delta_{exp}$ for ethyl 1-(methyl-*d*)piperidine-2-carboxylate was determined. Methyl derivative was computed to reduce conformational complexity.

Results and Discussion

We studied eight 2-substituted 1-(methyl-*d*)piperidines. For each piperidine, four possible stereoisomers (denoted as ***eq*-CH_2D-*eq*-2-R**, ***eq*-CH_2D-*ax*-2-R**, ***ax*-CH_2D-*eq*-2-R**, and ***ax*-CH_2D-*ax*-2-R**) were computed, and mole fractions for the three corresponding rotamers, **S**, **F**, and **A** were derived (**Figure 2**). A summary of our results is reported in **Table 1**.

For 2-isopropyl-1-(methyl-*d*)piperidine and 2-methyl-1-(methyl-*d*)piperidine, 0.94 of the fractional population of states exists as ***eq*-CH_2D-*eq*-2-R**, consistent with previous reports (**Table 1,** entries I, II).[9] In this stereoisomer, a rotameric preference for the deuteron in position **S** is observed. The origin of this isotope effect is primarily due to an n→σ* hyperconjugation interaction between the nitrogen lone-pair and an *anti* C-H(D) σ bond in the CH_2D group.[7,25] This stereoelectronic effect serves to weaken the *anti* C-H(D) bond relative to the *gauche* positions. Evidence of this weakening is observed in the computed stretching frequencies. For example, in 2-isopropyl-1-(methyl-*d*)piperidine (**Table 1**, entry I), the computed *anti* C-H stretching frequency (2957 cm^{-1}) is significantly lower than those associated with the gauche positions (3165 cm^{-1}, asymmetrical stretch; 3112 cm^{-1}, symmetrical stretch). To maximize zero-point vibrational stabilization in the molecule, deuterium partitions into the *gauche* C-H(D) bonds (i.e., position **S** or **F**). A smaller steric isotope effect, originating from interactions between the 2-substituent and vicinal C-H(D), results in further sequestering of deuterium into position **S**. Predicted Δδ values of 22.9 ppb and 13.2 ppb are computed for 2-isopropyl and 2-methyl substituted piperidines, respectively, consistent with experiments ($\Delta\delta_{exp}$ = 13.5 ± 0.4 ppb for 2-methyl-1-(methyl-*d*)piperidine).[23]

For 2-trifluoro-1-(methyl-*d*)piperidine, the dominant fractional population of 0.57 exists as ***eq*-CH_2D-*eq*-2-R**. However, a smaller but significant fractional population of 0.35 exists as ***eq*-CH_2D-*ax*-2-R** (**Table 1,** entry III). We attribute this distribution to a competing stabilizing hyperconjugation between the *N* lone pair and the *anti* C-C σ* orbital at the 2-position (i.e., the anomeric effect,[26] see **Figure 5**). We observe a weakened rotameric asymmetry, caused by a diminished lone pair-CH_2D interaction, and a smaller proton chemical shift difference in these species. $\Delta\delta_{comp}$ of 6.9 is computed for 2-trifluoro-1-(methyl-*d*)piperidine, consistent with experiments ($\Delta\delta_{exp}$ = 7.1 ± 0.4 ppb).

For 2-ethynyl-1-(methyl-*d)*piperidine, 2-fluoro-1-(methyl-*d)*piperidine and 2-phenyl-1-(methyl-*d)*piperidine, we observe a switch in stereoisomeric preference as the dominant fractional population exists as ***eq*-CH_2D-*ax*-2-R** (0.76, >0.99, and 0.67, respectively. See **Table 1**, entries IV, VI, and VII). Relatively small $\Delta\delta_{comp}$ values of 4.7, 1.3 and 0.3 ppb are computed for 2-ethynyl, 2-fluoro, and 2-phenyl substituted piperidines. The $\Delta\delta_{exp}$ for 2-phenyl-1-(methyl-*d)*piperidine was not experimentally observed, suggesting that the magnitude is <1 ppb.

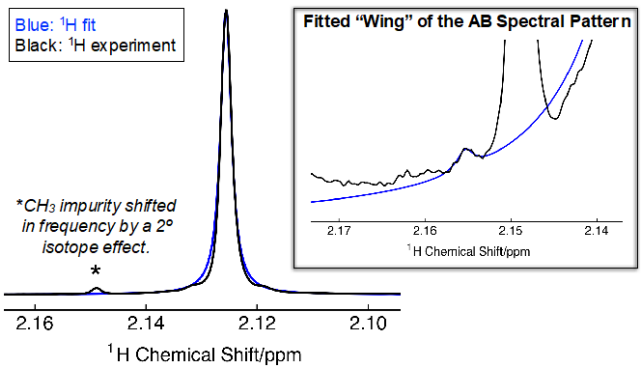


Figure 3. The small chemical shift difference for ethyl 1-(methyl-*d*)piperidine-2-carboxylate is estimated *via* a least-squares fitting of the experimental spectrum using Δδ (2.2 ± 0.6 ppb) and ^2J (11.7 Hz) as adjustable parameters.[27]

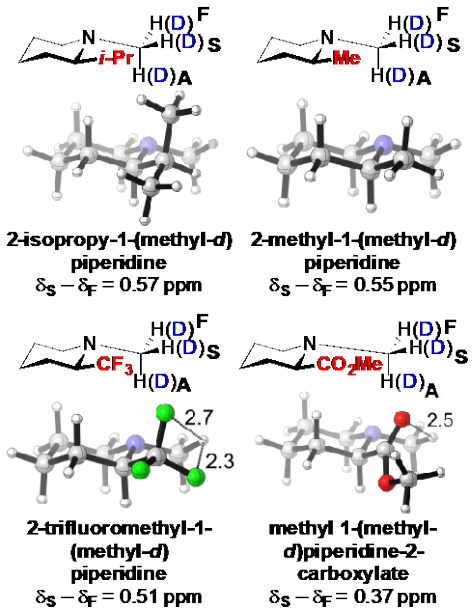


Figure 4. Difference in shielding constants at the S and F positions in the dominant stereoisomer of four 2-substituted 1-(methyl-*d*)piperidine. Optimized structures are illustrated using CYLview,[28] with distances reported in Ångströms.[24]

The dominant fractional population of stereoisomers in methyl 1-(methyl-*d*)piperidine-2-carboxylate exists as ***eq*-CH$_2$D-*eq*-2-R** (**Table 1,** entry V) as seen in the 2-isopropyl, 2-methyl, and 2-trifluoromethyl substituted derivatives (**Table 1,** entries I, II, and III). However, the magnitude of computed and experimentally observed Δδ for methyl 1-(methyl-*d*)piperidine-2-carboxylate is relatively small ($\Delta\delta_{comp.}$ = 2.6 ppb, $\Delta\delta_{exp.}$ = 2.2 ± 0.4 ppb). Measurement of such small chemical shift differences necessitated a least-squares fitting procedure in which the low-intensity outer lines of the AB quartet are fit using Δδ and ^2J as adjustable parameters. (**Figure 3**).[27] The origin of this deviation can be seen by comparing the difference in shielding constants between a proton at the **S** and **F** rotameric positions (i.e., $\delta_S - \delta_F$) of the dominant stereoisomer in the four species (**Figure 4**). The relatively small $\delta_S - \delta_F$ value for methyl 1-(methyl-*d*)piperidine-2-carboxylate may be ascribed to a CH•••O interaction[29] between the ester carboxyl oxygen and an N-methyl H (or D), which contributes to deshielding effects at the **S** position, thereby, reducing the overall difference in magnetic environment between the H_R and H_S protons.[30]

In the case of 2-*tert*-butyl-1-(methyl-*d*)piperidine, the dominant fractional population of 0.86 exists as ***ax*-CH$_2$D-*eq*-2-R** (**Table 1,** entry VIII). This stereoisomeric preference can be readily explained by the difference in A-values of methyl and *tert*-butyl ring substituents.[31] Furthermore, ***eq*-CH$_2$D-*eq*-2-R** is disfavored over the most stable stereoisomer by 2.4 kcal/mol due to a more severe *t*-Bu/Me gauche interaction. Interestingly, in the preferred stereoisomer, we still observe a rotameric preference for deuterium in the **S** position over the **F** (or **A**) position, suggesting that the *t*-Bu is bulky enough to affect the isotopically-perturbed system as seen in previous cases above. A Δδ of –10.2 ppb is predicted through computations. The negative Δδ stems from the computed proton chemical shifts at the CH$_2$D rotameric positions (**S**, **F**, and **A**) in ***ax*-CH$_2$D-*eq*-2-R** with respect to those in ***eq*-CH$_2$D-*eq*-2-R**. In 2-*tert*-butyl-1-(methyl-*d*)piperidine, where ***ax*-CH$_2$D-*eq*-2-R** is dominant, **S** = 2.29, **F** = 1.81, and **A** = 2.41 ppm, while in ***eq*-CH$_2$D-*eq*-2-R**, **S** = 2.73, **F** = 1.93, and **A** = 1.75 ppm.[23] The shielding of **A** with respect to **S** and **F** in the former is switched in the latter, resulting in a switch in sign of Δδ.

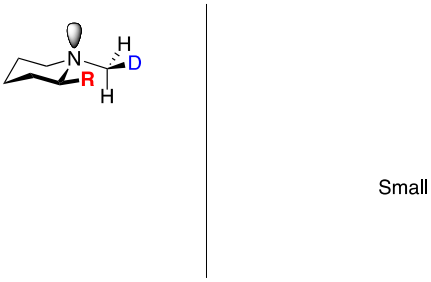
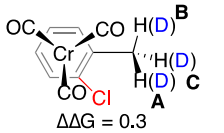


Figure 5. Qualitative model for evaluating small chemical shift differences in 2-substituted 1-(methyl-*d*)-piperidines.

Considering the results above, we build on the model previously established for evaluating and predicting equilibrium isotope effects and diastereotopic chemical shift differences in 2-substituted 1-(methyl-*d*)piperidines. Specifically, we add that the stereoisomeric relationship between the CH$_2$D group and 2-substituents is crucial. Non-polar and large alkyl substituents at the *2*-position tend to favor the equatorial position. For these cases, the previously-established model holds true. Polar, small groups, however, show an increased preference for the axial position due to anomeric effects. The competing orbital interaction between the lone pair on the piperidine nitrogen and the σ* of both methyl C-H(D) and 2-C-R bonds weakens the rotameric asymmetry, leading to a reduced Δδ (**Figure 5**).

Table 2. Mole fractions (χ) of CH$_2$D rotamers across conformers, and corresponding computational (comp) and experimental (exp) chemical shift differences (Δδ) between prochiral CH$_2$D protons in tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0). All experimental NMR spectra provided in the Supporting Information.[32]



Averaged Chemical Shift Differences (Δδ, H_R-H_S) *in ppb*

χ_A	χ_B	χ_C	χ_A	χ_B	χ_C	$\Delta\delta_{comp}$	$\Delta\delta_{exp}$ [a]
0.125	0.122	0.116	0.218	0.214	0.205	12.1	8.0

[a] Experimentally determined chemical shifts reported to ± 0.4 ppb precision.

Next, we compute the proton chemical shift difference in the CH_2D group of tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0) (**Figure 1**). It is known that coordination of metals to arenes results in a dramatic withdrawal of electron density from the arene and enhanced acidity of benzylic protons.[33,34] The $Cr(CO)_3$ moiety of tricarbonyl(1-chloro-2-deuteriomethylbenzene) chromium(0) facilitates dissociation at the benzylic group, provides facial selectivity on the arene ring, and stabilizes both benzylic cations and anions formed as reactive intermediates.[35–37] It is conceivable that the asymmetry in the complex could be coupled with selective C-H(D) bond weakening induced by the $Cr(CO)_3$ moiety to generate a small but observable CH_2D proton chemical shift difference. In fact, Siegel and Restelli previously reported chirotopicity of the methyl group in tricarbonyl(1-chloro-2-deuteriomethylbenzene) chromium(0).[10] An experimentally-observed chemical shift difference of 8.0 ± 0.4 ppb is observed in benzene between the CH_2D protons, consistent with their findings.[6]

The protocol for computing the Δδ in the 2-substituted 1-(methyl-*d*)piperidine study (*vide supra*) was also employed here. However, the PCM for dichloromethane was substituted with that of benzene to best align with experimental conditions. We located two isomers of tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0), one of which has a carbonyl bisecting the *ortho* methyl and chloro substituents (**Table 2**). A slight thermodynamic preference is observed for the bisecting conformer (ΔΔG = 0.3 kcal/mol). However, both conformers are predicted to equilibrate readily at room temperature ($\Delta G^{\ddagger}$ = 2.1 kcal/mol from lowest energy conformer).[23] When computing Δδ, we included the weighted chemical shift of the rotamers in each conformer. A Δδ of 12.1 ppb is predicted, in reasonable agreement with experiments.

Conclusion

In conclusion, we have shown that in the 2-substituted 1-(methyl-*d*)piperidine family, stereoelectronic effects of the 2-substituents on the piperidine ring strongly influence proton chemical shift differences. The polarity and size of the 2-substituent affects the 1,2-stereoisomeric relationship and consequently the strength of the rotational asymmetry within the CH_2D group. Furthermore, our tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0) results suggest that computational predictions of these small proton shift differences can be extended to a wider variety of CH_2D-containing compounds. We continue to investigate related species in our laboratories, and hope that this study aids the future synthesis and development of molecular agents bearing accessible long-lived states.

Experimental Section

General. Chemicals including labelled materials were purchased from Aldrich Chemical Co. and used without further purification. All reactions were performed in an inert argon or nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O solution using a Bruker DPX 400 (400 MHz and 101 MHz respectively) spectrometers. All spectra were reprocessed using ACD/Labs software version: 2014. Electron impact (EI) low resolution mass spectra were recorded on a Trace 2000 Series GC-MS. Electrospray (ES) low resolution mass spectra were recorded on a Waters ZMD or Waters TQD quadrupole spectrometer. Newly developed syntheses of 2-ethynylpiperidine[38] and 2-phenylpiperidine,[39] both known compounds, will be reported elsewhere.

2-Ethyl-1-(methyl-*d*)piperidine. To 2-ethylpiperidine (500 mg, 4.42 mmol) was added formaldehyde (1.08 mL of 37 wt. % in H_2O, 568 mg, 13.2 mmol, 3.0 equiv) followed by careful addition of formic acid-d_2 (0.83 mL of 95 % in D_2O, 22.0 mmol, 5.0 equiv), and the reaction heated at 85 °C (using a water bath) for 3 h. The reaction was cooled to rt, water (4 mL) added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x 5). The combined Et_2O extractions were dried ($MgSO_4$) and concentrated on a rotary evaporator without vacuum (bath temp = 40 °C) to give the title compound as a pale yellow clear oil (447 mg, 3.49 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (br d, *J* = 11.5 Hz, 1H), 2.28 - 2.15 (m, 2H), 2.11 - 2.01 (m, 1H), 1.82 - 1.68 (m, 2H), 1.68 - 1.53 (m, 4H), 1.46 - 1.35 (m, 1H), 1.34 - 1.18 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.0, 57.3, 42.7 (t, $J_{D,C}$ = 20.54 Hz, CH_2D), 30.1, 26.0, 25.5, 24.5, 9.4 ppm; MS EI (m/z) 84.04 [$C_5H_{10}N^{+\cdot}$] (70%) 49.1 (100%). HRMS (ES$^+$) for $C_8H_{17}DN$ calculated 129.1497, found 129.1497 Da.

2-Methyl-1-(methyl-*d*)piperidine. To 2-methylpiperidine (844 mg, 1.00 mL, 8.51 mmol) was added formaldehyde (37 wt. % in H_2O, 2.07 mL, 25.5 mmol, 3.0 equiv) followed by careful addition of formic acid-d_2 (95 % in D_2O, 1.72 g, 1.41 mL, 34.0 mmol, 4.0 equiv), and the reaction heated at 85 °C (using a water bath) for 3 h. The reaction was cooled to rt, water (2 mL) was added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x 5). The combined Et_2O extractions were dried ($MgSO_4$) and concentrated on a rotary evaporator without vacuum (bath temp = 40 °C) to give a pale yellow oil. Purification by Kugelrohr distillation (oven temperature 150 - 160 °C) to give the title compound as a clear oil (696 mg, 6.09 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 - 2.76 (m, 1H), 2.18 (d, $J_{H,D}$ = 1.0 Hz, 2H), 2.01 - 1.95 (m, 1H), 1.88 - 1.80 (m, 1H), 1.70 - 1.48 (m, 4H), 1.29 - 1.16 (m, 2H), 1.04 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.3, 57.0, 42.9 (t, $J_{D,C}$ = 20.5 Hz, CH_2D), 34.6, 26.1, 24.5, 20.2 ppm. MS EI (m/z) 84.07 [$C_5H_{10}N^{+\cdot}$] (60%).

2-Trifluoromethyl-1-(methyl-*d*)piperidine. To 2-trifluoromethylpiperidine (970 mg, 6.33 mmol), was added formaldehyde (1.54 mL of 37% in H_2O, 18.99 mmol, 3.0 equiv) followed by careful addition of formic acid-d_2 (1.2 mL, 31.7 mol, 5.0 equiv). The reaction was heated at 85 °C (using a water bath) for 4 h before being cooled to rt. Water (2 mL) was added and the acidic aqueous reaction extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x 5). The combined Et_2O extractions were dried (Na_2SO_4) and concentrated on a rotary evaporator without vacuum (bath temp = 40 °C). This gave the title compound as a colourless oil (948 mg, 5.64 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (dq, *J* = 11.9, 4.3 Hz, 1H), 2.68 - 2.59 (m, 1H), 2.39 (q, *J* = 1.8 Hz, 2H), 2.27 (dt, *J* = 11.8, 6.8 Hz, 1H), 1.88 - 1.82 (m, 1H), 1.78 - 1.71 (m, 1H), 1.66 - 1.55 (m, 3H), 1.37 - 1.27 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 126.7 (q, *J* = 285.4 Hz), 63.9 (q, *J* = 25.7 Hz), 55.7, 44.0 (tq, *J* = 20.5, 2.2 Hz), 25.2 (q, *J* = 3.0 Hz), 25.0, 22.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ 68.4 ppm; MS ESI$^+$ (m/z) 169.28 $[M+H]^+$. HRMS (ES$^+$) for $C_7H_{12}DF_3N$ calculated 169.1057, found 169.1059 Da.

2-Ethynyl-1-(methyl-*d*)piperidine. To 2-ethynylpiperidine (70 mg, 0.64 mmol) was added formaldehyde (157 µL of 37 wt. % in H_2O, 58 mg, 1.93 mmol, 3.0 equiv) followed by careful addition of formic acid-d_2 (120 µL of 95 % in D_2O, 3.20 mmol, 5.0 equiv), and the reaction heated at 85 °C (using a water bath) for 3 h. The reaction was cooled to rt, water (1 mL) added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x 5). The combined Et_2O extractions were dried ($MgSO_4$) and concentrated on a rotary evaporator without vacuum (bath temp = 40 °C) to give the title compound as a pale yellow oil (67 mg, 0.54 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 - 3.33 (m, 1H), 2.63 -2.48 (m, 1H), 2.37 - 2.27 (m 4H), 1.87 - 1.71 (m, 2H), 1.68 - 1.42 (m, 4H) ppm; MS EI (m/z) 124 .0 $[M^{+\cdot}]$ (20%). ^{13}C NMR (101 MHz, $CDCl_3$) δ 77.2, 73.5, 68.0, 53.8, 43.9 (t, $J_{D,C}$ = 20.5 Hz, CH_2D), 31.5, 25.6, 20.5 ppm; MS EI (m/z) 124 .0 $[M^{+\cdot}]$ (20%). HRMS (ES$^+$) for $C_8H_{13}DN$ calculated 125.1184, found 125.1183 Da.

Ethyl 1-(methyl-*d*)piperidine-2-carboxylate. To ethylpipecolinate (980 mg, 6.24 mmol) was added formaldehyde (1.50 mL of 37 wt. % in H_2O, 568 mg, 19.08 mmol, 3.0 equiv) followed by careful addition of formic acid-d_2 (1.20 mL of 95 % in D_2O, 31.80 mmol, 5.0 equiv), and the reaction heated at 85 °C (using a water bath) for 3 h. The reaction was cooled to rt, water (2 mL) added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x5). The combined Et_2O extractions were dried ($MgSO_4$) and concentrated on a rotary evaporator without vacuum (bath temp = 40 °C) to give the title compound as a clear oil (977 mg, 5.68 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.1 Hz, 2H), 3.00 - 2.84 (m, 1H), 2.68 (dd, *J* = 10.3, 3.2 Hz, 1H), 2.20 (br s, 2H), 2.13 - 1.96 (td, *J* = 11.2, 3.9 Hz, 1H), 1.86- 1.55 (m, 5H), 1.34 - 1.23 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 67.9, 60.5, 55.0, 43.9 (t, $J_{D,C}$ = 20.5 Hz, CH_2D), 29.7, 25.1, 22.9, 14.2 ppm; MS ESI$^+$ (m/z) 173.3 $[M+H]^+$. HRMS (ES$^+$) for $C_9H_{17}DNO_2$ calculated 173.1395, found 173.1395 Da.

2-Phenyl-1-(methyl-*d*)piperidine. To 2-phenylpiperidine (1.00 g, 6.21 mmol), formaldehyde (1.51 mL of 37% in H_2O, 18.63 mmol, 3.0 equiv) was added followed by careful addition of formic acid-d_2 (1.17 mL of 95 % in D_2O, 31.05 mmol, 5.0 equiv). The reaction was heated at 85 °C (using a water bath) for 4 h before being cooled to rt. Water (2 mL) was added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x 5). The combined Et_2O extractions were dried (Na_2SO_4) and concentrated on a rotary evaporator without vacuum (bath temp = 40 °C). This gave the title compound as a yellow oil (921 mg, 5.23 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 - 7.18 (m, 5H) 2.99 (br d, 1H, *J* = 11.6), 2.71 (dd, 1H, *J* = 11.0, 3.0 Hz), 2.10 - 2.05 (m, 1H), 1.95 (s, 2H), 1.83 - 1.12 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 128.4, 127.4, 126.9, 71.2, 57.5, 45.6 (t, $J_{D,C}$ = 20.5 Hz, CH_2D), 35.9, 26.2, 25.0 ppm; MS ESI$^+$ (m/z) 177.3 $[M+H]^+$. HRMS (ES$^+$) for $C_{12}H_{17}DN$ calculated 177.1497, found 177.1499 Da.

α-Deuterio-*o*-chlorotoluene.[40] To 2-chlorobenzyl bromide (2.00 g, 9.73 mmol) in DMSO-d_6 (6 mL) at 0°C was added sodium borodeuteride (0.82 g, 19.46 mmol) portion-wise. The reaction formed a white solid that was stirred for 4 h at rt. The reaction was quenched with methanol (0.75 mL), Et_2O was added and the organic layer washed with H_2O (x3), brine and then dried ($MgSO_4$). The solvent was removed *in vacuo* at rt. The resultant oil was purified by Kugelrohr distillation to give the title compound as a colourless oil (0.89 g, 6.98 mmol, 72%). Bpt 157-159°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (dd, *J* = 7.1, 1.7 Hz, 1H), 7.27 - 7.12 (m, 3H), 2.41 - 2.37 (t, J_{HD} = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.0, 134.4, 130.9, 129.0, 127.1, 126.5, 19.7 ppm (t, J_{CD} = 19.8 Hz). GC-MS (EI) m/z (100%) 126.8 $C_7H_6DCl^{+\cdot}$, 91.9 $C_7H_6D^{+\cdot}$.

Tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0).[41] α-Deuterio-*o*-chlorotoluene (**1**, 0.38 g, 3.0 mmol) and hexacarbonyl chromium(0) (0.33 g, 1.5 mmol) in dibutyl ether/THF (9:1, 7.5 mL) was heated at reflux for 36 h. The reaction was allowed to cool, Et_2O was added and the solution passed through a short column of alumina, eluting with Et_2O. The solvent was removed *in vacuo* and the crude yellow solid recrystallized from Et_2O/pentane and the yellow crystals washed with cold pentane. The title compound was obtained as a yellow crystalline solid (0.28 g, 1.06 mmol, 35%). Mpt 100-102°C. ^{1}H NMR (400 MHz, C_6D_6) δ = 4.75 (br d, *J* = 6.2 Hz, 1H), 4.30 (br d, *J* = 6.0 Hz, 1H), 4.18 (br t, *J* = 6.1 Hz, 1H), 4.07 (br t, *J* = 6.1 Hz, 1H), 1.71 (br s, 2H); ^{13}C NMR (101 MHz, C_6D_6) δ = 112.0, 106.3, 93.9, 93.3, 91.0, 90.4, 19.0 ppm (t, J_{CD} = 19.9 Hz). GC-MS (EI) m/z (100%) 126.8 $C_7H_6DCl^{+\cdot}$.

Sample Preparation. 2-Substituted 1-(methyl-*d)*-piperidines were dissolved in 0.5 mL of CD_2Cl_2 to a concentration of 0.1 M. 12.58 mg of tricarbonyl(1-chloro-2-deuteriomethylbenzene)chromium(0) was dissolved in 0.5 mL of C_6D_6 to a concentration of 0.1 M. TMS vapor was added to all samples as a reference compound.

ASSOCIATED CONTENT

Supporting Information. Computational protocols, benchmark studies, shielding constants, coordinates, energies, vibrational frequencies, experimental ^{1}H, ^{13}C, and, where appropriate, ^{19}F NMR spectra.

AUTHOR INFORMATION

Corresponding Author

daniel.o'leary@pomona.edu

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