Communication

Fomenting Proton Anisochronicity in the CHD Group

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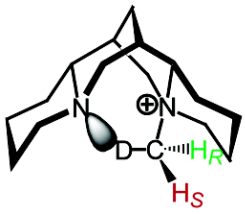

$\Delta\delta(H_R - H_S)$ = 106 ppb @ 400 MHz

1:4 $CD_3OD/CDFCl_2$, –110 °C

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Fomenting Proton Anisochronicity in the CH_2D Group

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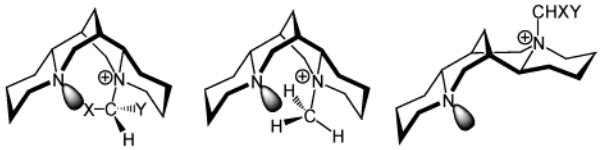
The stereogenic methyl group CHDT has afforded valuable insights into enzymatic methyl transfer mechanisms by offering a stereochemical configuration to be analyzed where none would exist for the CH_3 group.[1] While these advances have relied on kinetic isotope effects to assign the configuration at a stereogenic methyl center, isotopic labeling is known to perturb NMR-observable equilibria as well.[2,3] To this end, two molecules have been shown to induce anisochronous chemical shifts for the diastereotopic protons of the monodeutero methyl group CH_2D.[4,5] The effect usually occurs via a confluence of two factors: (1) an asymmetric population distribution for methyl rotation, and (2) disparate chemical shifts for each static methyl hydrogen position. This concept has been exploited to assign the configuration and enantiomeric purity of a stereogenic methyl group using tritium NMR spectroscopy.[6]

In the published examples, population asymmetry arises through the selective weakening of a single methyl C−H (or C−D) bond, resulting in vibrational destabilization of the conformer for which the deuteron participates in the weakened bond.[3,4] However, the efficacy of this destabilization is tempered by the molecule's relative indifference with respect to the placement of deuterium in either of the strong bonds; the observed chemical shift difference between the CH_2D protons is significantly reduced through averaging of these nearly degenerate conformations. Ideally, a single methyl rotamer would be favored over all others.



The (*N*-methyl)-α-isosparteinium cation **Ia** offers a solution. Fourier-mapped crystal structures,[7] IR analysis,[8] and ab initio optimized structures[9,10] indicate that the bridging conformation **Ia** is thermodynamically favored over other possibilities such as the bifurcated form **II**. The presence of the geminal electron-withdrawing quaternary nitrogen center and the geometry of the interaction cause us to designate it as a C−H···N hydrogen bond;[11] calculated methyl stretching frequencies for **Ia** are consistent with a classical hydrogen bond.[12]

Vibrational zero-point energies, excited-state energies, and entropies computed[13,14] at the B3LYP/6-31G(d) level of theory indicate that, in the *N*-CH_2D compound **Ib**, deuterium is preferred in the bridging position **IIIa** over the other two possible bridged rotamers **IIIb** and **IIIc** (Figure 1) by free energy differences of 28 and 56 cal/mol, respectively, at 25 °C.[15−17] A triangular equilibrium for rotation of the CH_2D group (Figure 1) was solved using these free energy differences to yield theoretical mole fractions of 0.349, 0.333, and 0.318 for rotamers **IIIa**, **IIIb**, and **IIIc**.

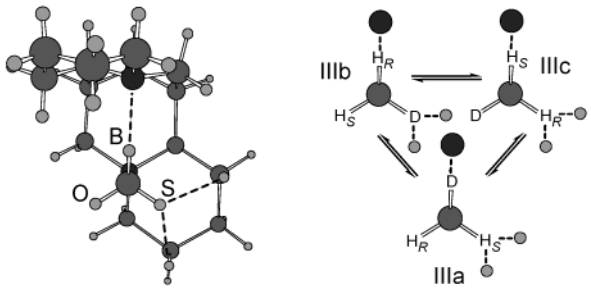


Figure 1. At left: a view of (*N*-methyl)-α-isosparteinium that illustrates bridging to the opposing nitrogen (**B**) and 1,3 diaxial steric interactions (**S**) for the *N*-methyl group. One ring was deleted for clarity. At right: a triangular equilibrium between the three possible bridging rotamers of (*N*-CH_2D)-α-isosparteinium.

Computed isotropic magnetic shielding values at the HF/6-311G+(2d,p) level give limiting chemical shifts of 6.96, 2.90, and 1.84 ppm at positions **B**, **S**, and **O** (Figure 1) as compared to the protons of TMS computed at the same theoretical level. These limiting chemical shifts were weighted by the mole fractions calculated above to yield theoretical averaged chemical shifts of 3.879 and 3.835 ppm for the *pro-R* and *pro-S* hydrogens of (*N*-CH_2D)-α-isosparteinium and a chemical shift difference of 44 ppb. Application of the same computational procedure to α-deutero-1,2-dimethylpiperidine yielded a chemical shift difference of 17 ppb, comparable with the experimental value of 14 ppb.[4]

(−)-Isosparteine[18] was methylated with CH_2DI in acetone at 60 °C for 3 h to give **Ib** in 83% yield. An initial ^{1}H NMR spectrum of compound **Ib** in CD_3OD agreed surprisingly well with our theoretical predictions. The AB quartet for the *pro-R* and *pro-S* protons of the CH_2D group (Figure 2A) yielded a chemical shift difference of 43 ppb at 22 °C, as compared to the theoretical prediction of 44 ppb. The acute temperature dependence of this effect is best illustrated by the ^{1}H spectrum of the compound at −110 °C in 1:4 $CD_3OD/CDFCl_2$[19] (Figure 2B): the observed chemical shift difference of this sample was 106 ppb.

The nature of the observed effect was probed by comparing the isotope shift between compounds **Ib** and **Ia** to that between the *exo*-(*N*-methyl)-sparteinium[20] isotopomers **IVb** and **IVa** as a function of temperature. Spectra of all three proton-containing isotopomers were recorded in the same sample tube for each compound (Figure 2C and D), and the isotope shifts between the CH_3 forms (**Ia** and **IVa**) and the monodeutero CH_2D forms (**Ib** and **IVb**) were measured over a range of temperatures (Figure 3). As the populations of the nondegenerate rotational conformers **IIIa**, **IIIb**, and **IIIc** of structure **Ib** vary with temperature, so should the isotope shift $\delta_H(CH_3) - \delta_H(CH_2D)$ for **Ia** and **Ib**. The *pro-R*/*S* chemical shift difference and the two-bond isotope shift for the CH_2D protons of **Ib** were found to increase linearly with decreasing temperature, consistent with an equilibrium isotope effect (Figure 3). In contrast, the small positive temperature dependence of the isotope shift for **IVb** is consistent with a purely intrinsic isotope

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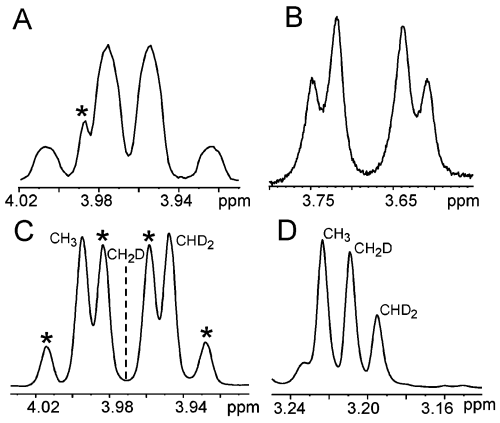

Figure 2. (A) ^{1}H spectrum of compound **Ib** in CD_3OD at 22 °C; the AB chemical shift separation is 43 ppb. Residual coupling to the geminal deuteron and quaternary ^{14}N is observed as a broadening of the quartet lines; a trace of **Ia** (*) was added as a reference. (B) ^{1}H spectrum of compound **Ib** in 1:4 $CD_3OD/CDFCl_2$ at −110 °C with an AB chemical shift separation of 106 ppb. (C) $^1H\{^2H\}$ spectrum at 30 °C of **Ia**, **Ib**, and **Ic** in 7:1 CD_2Cl_2/CD_3OD. The peaks of the AB quartet for compound **Ib** are indicated with *; the center of the AB is indicated with a dotted line. (D) $^1H\{^2H\}$ spectrum at 30 °C of **IVa**, **IVb**, and **IVc** in 7:1 CD_2Cl_2/CD_3OD. All spectra were obtained on a Bruker DPX 400 MHz spectrometer.

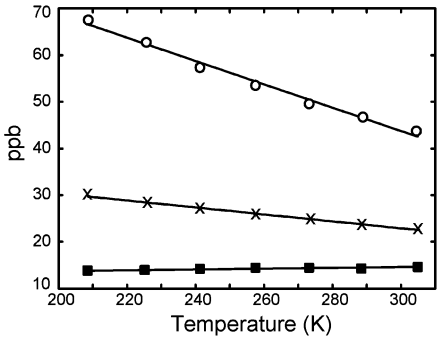

Figure 3. The experimental temperature dependence of the *pro-R*/*S* chemical shift difference and two-bond isotope shifts for **Ib** and **IVb** in ppb. Spectra were taken at 400 MHz in 7:1 CD_2Cl_2/CD_3OD.[22] (○): The experimental chemical shift difference between the CH_2D protons of **Ib**. (×): The two-bond isotope shift $\delta_H(CH_3) - \delta_H(CH_2D)$ for **Ia** and **Ib**. (■): The two-bond isotope shift for **IVa** and **IVb**.

effect[21] (Figure 3). On the basis of this comparison, it seems reasonable to attribute the observed splitting effect to the interactions between the methyl group and the nitrogen lone pair, which are present in **Ib** but absent in **IVb**.

On the basis of the 3-fold increase in CH_2D chemical shift separation for **Ib** relative to α-deutero-1,2-dimethylpiperidine, the procedure outlined herein may provide an improved method for assigning the configuration and enantiomeric purity of stereogenic methyl groups by ^{3}H NMR spectroscopy.[6] According to the ab initio calculations described above, the *R*- and *S*-CHDT methyl groups in methylated (−)-isosparteine are expected to exhibit tritium NMR chemical shifts that differ by 49 ppb, with the *S*-CHDT group giving rise to the downfield resonance. These predictions will be tested in collaboration with Cintrat et al., who have discovered an improved route to the methylating agent (*N*-CHDT)-*N*,*N*-ditosylamine.[23] The details of these experiments will be disclosed in a forthcoming paper.

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