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^1H and ^{13}C NMR Assignments for (*N*-methyl)-(-)-(α)-Isosparteinium Iodide and (*N*-methyl)-(-)-Sparteinium Iodide

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Keywords: NMR, ^1H , ^{13}C , lupine alkaloids, quinolizidine, sparteine, isosparteine, (*N*-methyl)-sparteinium, (*N*-methyl)-isosparteinium, sparteine methiodide, isosparteine methiodide, DFT shielding calculations, DFT proton-proton coupling constant calculations

Introduction

(-)-Sparteine (**1**) and (-)-(α)-isosparteine (**2**) are members of the lupine alkaloid family.^[1-2] Sparteine has found extensive use in asymmetric organic transformations, including lithiations^[3] and Pd-catalyzed oxidations.^[4-7] (α)-Isosparteine, which can be made from sparteine, has been utilized as a chiral ligand for a limited number of stereoselective reactions.^[8-9] The two compounds differ in that **1** displays an *exo-endo* arrangement of the bridgehead hydrogens at C-11 and C-6, respectively, while **2** retains an *exo-exo* arrangement of these atoms (Figure 1). This study is focused on assigning ^1H chemical shifts and coupling constants and ^{13}C chemical shifts for *N*-methyl derivatives of sparteine and isosparteine, both of which have been fully characterized by X-ray crystallography. X-ray analysis of (*N*-methyl)-(-)-sparteinium iodide (**3**) revealed a chair-chair-boat-chair conformation (Figure 1),^[10-11] and its ^1H and ^{13}C NMR chemical shift assignments were reported by Duddeck and co-workers in 1995.^[12] An X-ray analysis of (*N*-methyl)-(α)-isosparteinium iodide (**4**) showed an all-chair conformation in which the N-CH_3 group is positioned in close proximity to the transannular nitrogen lone pair, resulting in a $^+\text{NCH}\cdots\text{N}$ hydrogen bond.^[13] Our group has harnessed the bridging geometry in **4** with an equilibrium isotope effect to investigate ^1H and ^3H chemical shift differences in (*N*- CH_2D) and (*N*- CHDT) isotopologs of **4**.^[14-15] Simeonov, Duddeck, and co-workers have previously reported ^1H and ^{13}C NMR chemical shift assignments for **4** dissolved in $\text{DMSO-}d_6$.^[16] We noticed discrepancies between our ^1H and ^{13}C assignments for **3** and **4** and values reported in the earlier studies. This was especially true for the ^1H data for **4**, where 16 out of 27 assignments differ from the previously reported values. Spectral assignments for **3** and **4** are also compared with quantum-mechanically computed ^{13}C and ^1H NMR chemical shifts^[17-21] to further validate the assignments reported here.

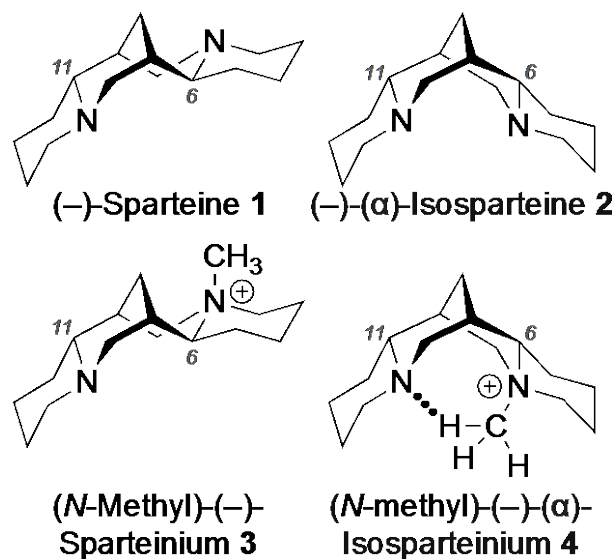


Figure 1. Structural representations, reflective of X-ray structures, for compounds **1-4**.

Results and Discussion

The complete assignment of ^{13}C and ^1H resonances for **4** and **3** was achieved through the use of standard 1D and 2D techniques as well as 1D TOCSY and 1D DPGSE NOE experiments. The experimental and computed ^{13}C and ^1H NMR assignments for **4** and **3**, along with previously reported assignments by Simeonov, et al. and Duddeck, et al. are presented in Tables 1 and 2, and Tables 3 and 4, respectively. Structural representations, B3LYP optimized geometries, and key NOE correlations are illustrated in Figures 2 and 3. An assignment strategy narrative, representative spectra, and computed ^1H and ^{13}C NMR chemical shifts and J coupling constants for **4** and **3** can be found in the Supporting Information.

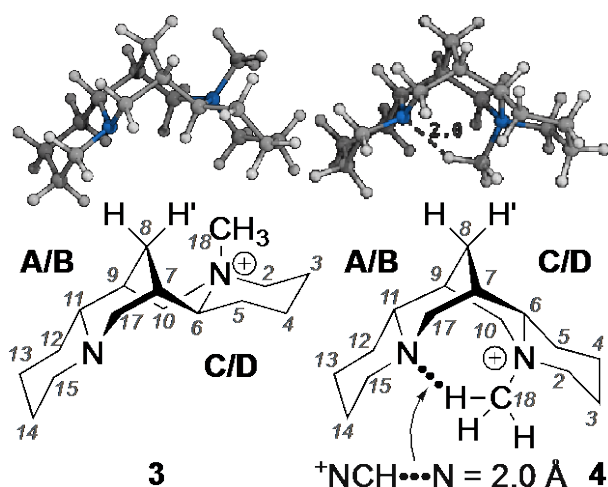


Figure 2. Lowest energy computed structures for **3** and **4** at the B3LYP/6-31G(d) level of theory.

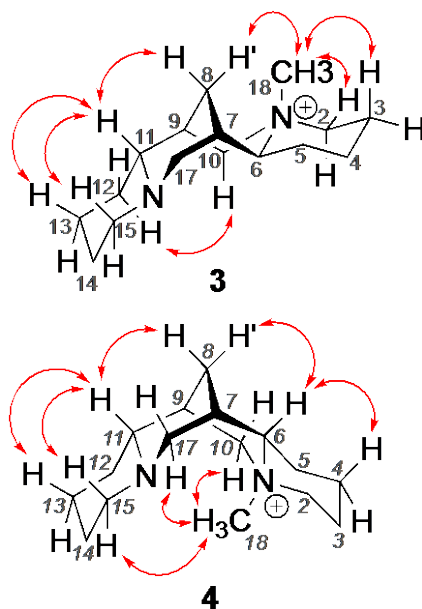


Figure 3. Key NOE correlations used for the structural assignment of compounds **3** and **4**.

(*N*-Methyl)-(-)-(α)-isosparteinium iodide (4**).** Discussed herein are those ^1H and ^{13}C assignments that differ from previously reported values. The H-8 protons, spanning the B/C ring system, were assigned through 2D ROESY and 1D DPGSE NOE data. For example, DPGSE selective excitation of H-11_{ax} (2.15 ppm) showed an Overhauser enhancement to H-8 at $\delta_{\text{H}} = 1.62$ ppm (Figure 4). H-8 also showed a strong COSY correlation, via a large geminal coupling, to H-8' at 2.01 ppm. The H-8' assignment was confirmed with observation of a strong NOE when H-6_{ax} was selectively excited in a DPGSE experiment, and the H-8 and H-8' assignments were also consistent with $^4J_{\text{W}}$ couplings, detected in 2D COSY and TOCSY spectra, to H-10_{eq} and H-17_{eq}, respectively. Simeonov and co-workers' H-8 and H-8' assignments were opposite to ours.

The assignment of H-17_{ax} and H-17_{eq}, each correlating to $\delta_{\text{C}} = 51.58$ ppm in the HSQC experiment, was done on the basis of a known stereoelectronic effect that shields H-17_{ax} because of hyperconjugation between the nitrogen lone pair and the antibonding σ^* C-H orbital.^[22] Thus, the more shielded resonance at $\delta_{\text{H}} = 2.22$ ppm was assigned to H-17_{ax} and the less shielded resonance at $\delta_{\text{H}} = 2.77$ ppm was assigned to H-17_{eq}. This assignment was confirmed through observing an NOE between the *N*-Me group and H-17_{eq}. In contrast, Simeonov and co-workers assigned the more shielded resonance to H-17_{eq}.

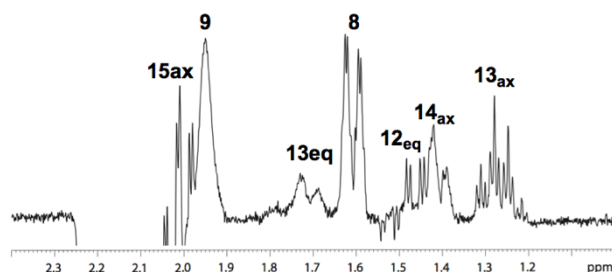


Figure 4. 400 MHz ^1H 1D DPGSE NOE spectrum for **4** with selective excitation of H-11_{ax}.

Resonances at 3.69 ppm (H-10_{eq}), 3.59 ppm (H-6_{ax}), and 3.39 ppm (H-10_{ax}), deshielded because of proximity to the quaternary nitrogen atom, were readily assigned on the basis of Overhauser and HSQC data. The remaining deshielded resonances for H-2_{ax} and H-2_{eq} formed a complex multiplet centered at $\delta_{\text{H}} = 3.42$ ppm and partially overlapped with the H-10_{ax} resonance. The C-2 ($\delta_{\text{C}} = 68.28$ ppm) and C-10 ($\delta_{\text{C}} = 64.04$ ppm) resonances were assigned through HSQC correlations with the assigned ^1H patterns. The H-2_{ax}/H-2_{eq}/H-10_{ax} multiplet was adequately simulated by using the DFT J values as a starting point, and the (visually) fit values were not significantly different (Table 2, Supporting Information). Using this approach, H-2_{ax} was assigned as deshielded ($\delta_{\text{H}} = 3.44$ ppm) relative to H-2_{eq} ($\delta_{\text{H}} = 3.40$ ppm). The more clearly delineated H-2_{ax} multiplet pattern was replicated using two large coupling constants (one a 12.5 Hz 2J coupling to H-2_{eq} and the other a 12.5 Hz anti 3J coupling to H-3_{ax}), and one small coupling constant (a 3.6 Hz gauche 3J coupling to H-3_{eq}). The H-2_{eq} multiplet was fit using the 12.5 Hz geminal H-2_{ax} coupling and smaller 3J gauche couplings to H-3_{ax} (5.2 Hz) and H-3_{eq} (1.8 Hz). In contrast with our analysis, Simeonov and co-workers assigned the resonances at $\delta_{\text{H}} = 3.69$ ppm to H-2_{ax}, $\delta_{\text{H}} = 3.43$ ppm to H-2_{eq}, $\delta_{\text{C}} = 64.05$ ppm to C-2, $\delta_{\text{H}} = 3.48$ ppm to H-10_{ax}, $\delta_{\text{H}} = 3.39$ ppm to H-10_{eq}, and $\delta_{\text{C}} = 68.17$ ppm to C-10.

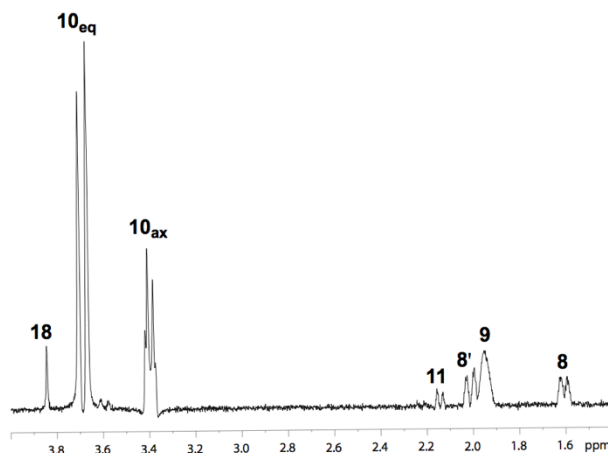


Figure 5. 1D TOCSY spectrum (80 ms spin lock) for **4** with selective excitation of H-10_{eq}.

The H-4_{eq} and H-4_{ax} resonances were assigned by observing a strong NOE between H-6_{ax} and H-4_{ax}. The previously assigned H-2_{ax} and H-2_{eq} were also correlated via 2D COSY with $\delta_{\text{H}} = 2.06$ ppm (1H, m, H-3_{ax}) and $\delta_{\text{H}} = 1.72$ ppm (1H, m, H-3_{eq}). The assignment of H-3_{ax} was

confirmed on the basis of an Overhauser effect between it and the *N*-Me group. In contrast with our assignments, Simeonov and co-workers assigned the peaks at $\delta_{\text{C}} = 19.32$ ppm and 21.93 ppm to C-4 and C-3, respectively, and also arrived at different ^1H shift assignments for their attached hydrogens (Table 2).

The relative shift assignment of H-15_{ax} (2.02 ppm, ddd, $J = 11.8, 11.8, 3.0$ Hz), and H-15_{eq} (2.73 ppm, br d, $J = 11.8$ Hz) is consistent with the expected splitting patterns and the stereoelectronic shielding effect discussed earlier. The assignment is further supported by NOEs between H-15_{eq} and the *N*-Me group, and between H-11_{ax} and H-15_{ax}. Simeonov and coworkers' H-15_{ax}/H-15_{eq} assignments were opposite to ours. A 1,3-diaxial NOE between H-11_{ax} and H-13_{ax} (1.26 ppm, dddd, $J = 12.7, 12.7, 12.7, 4.1, 4.1$ Hz) established the distal portion of the A ring, and the HSQC experiment provided an assignment for H-13_{eq} (1.75 ppm, br d, $J = 12.5$ Hz) and C-13 (24.17 ppm). Likewise, selective excitation of the H-13_{ax} resonance produced Overhauser effects at 1.75, 2.02 and 2.15 ppm, confirming the assignment of H-13_{eq}, H-15_{ax}, and H-11_{ax}, respectively. The H-12 resonances were assigned by locating a strong COSY correlation, mediated by a large anti coupling, between H-11_{ax} and $\delta_{\text{H}} = 1.50$ ppm (dddd, $J = 12.4, 12.4, 12.4, 3.6$ Hz, H-12_{ax}). The H-12_{ax} resonance also exhibited an Overhauser effect when the H-10_{eq} resonance was selectively excited. The HSQC experiment revealed H-12_{eq} ($\delta_{\text{H}} = 1.43$ ppm, m) and C-12 ($\delta_{\text{C}} = 28.81$ ppm). Simeonov and co-workers' H-12 assignments did not match ours (Table 2).

Table 1. Experimental ^{13}C chemical shifts for **4** from Simeonov et al., this work, and shifts computed at the mPW1W91/6-311+G(2d,p)/PCM(DMSO) level using B3LYP/6-31G(d) geometries. Bold entries indicate shifts not in agreement with values reported here.

^{13}C	$\delta_{\text{exp.}}$ (ppm) <i>Simeonov et al.</i>	$\delta_{\text{exp.}}$ (ppm) <i>This Work</i>	$\delta_{\text{comp.}}$ (ppm) <i>This Work</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc.}} $ <i>Simeonov et al.</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc.}} $ <i>This Work</i>
2	64.05	68.28	68.24	4.19	0.04
3	21.93	19.32	18.83	3.10	0.49
4	19.32	21.96	20.70	1.38	1.26
5	23.40	23.42	22.11	1.29	1.31
6	73.02	73.01	76.00	2.98	2.99
7	33.86	33.89	34.45	0.59	0.56
8	33.65	33.71	32.84	0.81	0.87
9	34.39	34.42	35.47	1.08	1.05
10	68.17	64.04	65.15	3.02	1.11
11	62.32	62.29	60.75	1.57	1.54
12	28.76	28.81	26.98	1.78	1.83
13	24.11	24.17	22.57	1.54	1.60
14	24.92	24.97	23.07	1.85	1.90
15	54.53	54.57	52.29	2.24	2.28
17	51.47	51.58	49.36	2.11	2.22
18	43.79	43.61	41.70	2.09	1.91

Table 2. Experimental ^1H chemical shifts for **4** from Simeonov et al., this work, and shifts computed at the mPW1W91/6-311+G(2d,p)/PCM(DMSO) level using B3LYP/6-31G(d) geometries. Bold entries indicate shifts not in agreement with values reported here.

^1H	$\delta_{\text{exp.}}$ (ppm) <i>Simeonov et al.</i>	$\delta_{\text{exp.}}$ (ppm, mult ^a) <i>This Work</i>	$\delta_{\text{comp.}}$ (ppm) <i>This Work</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc}} $ <i>Simeonov et al.</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc}} $ <i>This Work</i>
2ax	3.69	3.44^b m	3.19	0.50	0.25
2eq	3.43	3.40^b m	3.27	0.16	0.13
3ax	1.58	2.06 m	2.12	0.54	0.06
3eq	1.78	1.72 m	1.76	0.02	0.04
4ax	1.70	1.58 m	1.65	0.05	0.07
4eq	2.07	1.78 m	1.87	0.20	0.09
5ax	2.00	2.01 m	2.12	0.12	0.11
5eq	1.54	1.56 m	1.53	0.02	0.03
6ax	3.61	3.59 ddd	3.43	0.18	0.16
7eq	1.91	1.94 br m	1.87	0.04	0.07
8	2.01	1.62 br d	1.76	0.25	0.14
8'	1.59	2.01 br d	1.98	0.39	0.03
9eq	1.94	1.95 br m	1.87	0.07	0.08
10ax	3.48	3.39^b dd	3.27	0.21	0.12
10eq	3.39	3.69 ddd	3.60	0.21	0.09
11ax	2.15	2.15 ddd	2.30	0.15	0.15
12ax	1.39	1.50 dddd	1.53	0.14	0.03
12eq	1.54	1.43 m	1.42	0.12	0.01
13ax	1.26	1.26 ddddd	1.35	0.09	0.09
13eq	1.73	1.75 br d	1.76	0.03	0.01
14ax	1.39	1.42 ddddd	1.53	0.14	0.11
14eq	1.53	1.56 br d	1.53	0	0.03
15ax	2.72	2.02 ddd	2.12	0.60	0.10
15eq	2.00	2.73 br d	2.68	0.68	0.05
17ax	2.76	2.22 dd	2.35	0.41	0.13
17eq	2.20	2.77 ddd	2.84	0.64	0.07
18	3.85	3.85 s	4.11	0.26	0.26

^aNote: **4** $J(\text{Hz})$: $2_{\text{ax}}, 2_{\text{eq}} = 12.5^{\text{b}}$, $2_{\text{ax}}, 3_{\text{ax}} = 12.5^{\text{b}}$, $2_{\text{ax}}, 3_{\text{eq}} = 3.6^{\text{b}}$, $2_{\text{eq}}, 3_{\text{eq}} = 1.8^{\text{b}}$, $2_{\text{eq}}, 3_{\text{ax}} = 5.2^{\text{b}}$, $6_{\text{ax}}, 5_{\text{ax}} = 12.8$, $6_{\text{ax}}, 5_{\text{eq}} = 2.1$, $6_{\text{ax}}, 7_{\text{eq}} = 2.1$, $8, 8' = 12.3$, $10_{\text{ax}}, 10_{\text{eq}} = 13.8$, $10_{\text{ax}}, 9 = 4.2$, $10_{\text{eq}}, 9 = 1.8$, $10_{\text{eq}}, 8 = 1.8^{\text{b}}$, $11_{\text{ax}}, 12_{\text{ax}} = 12.4$, $11_{\text{ax}}, 12_{\text{eq}} = 2.6$, $11_{\text{ax}}, 9_{\text{eq}} = 2.6$, $12_{\text{ax}}, 12_{\text{eq}} = 12.4$, $12_{\text{ax}}, 13_{\text{ax}} = 12.4$, $12_{\text{ax}}, 13_{\text{eq}} = 3.6$, $13_{\text{ax}}, 13_{\text{eq}} = 12.7$, $13_{\text{ax}}, 14_{\text{ax}} = 12.7$, $13_{\text{ax}}, 12_{\text{eq}} = 4.1$, $13_{\text{ax}}, 14_{\text{eq}} = 4.1$, $14_{\text{ax}}, 14_{\text{eq}} = 12.5$, $14_{\text{ax}}, 15_{\text{ax}} = 12.5$, $14_{\text{ax}}, 15_{\text{eq}} = 3.9$, $14_{\text{ax}}, 13_{\text{eq}} = 3.9$, $15_{\text{ax}}, 15_{\text{eq}} = 11.8$, $15_{\text{ax}}, 14_{\text{eq}} = 3.0$, $17_{\text{ax}}, 17_{\text{eq}} = 12.2$, $17_{\text{ax}}, 7 = 4.2$, $17_{\text{eq}}, 7 = 1.9$, $17_{\text{eq}}, 8' = 1.9$.

^bNote: Parameters determined by simulation.

(*N*-Methyl)-(-)-sparteinium iodide (3). Duddeck and co-workers reported ^1H chemical shifts (but not coupling constants) and ^{13}C chemical shifts for (*N*-methyl)-(-)-sparteinium iodide **3** alongside ten other sparteine derivatives in 1995.^[12] Their assignments, which were reported using a different skeletal numbering system, have been converted to the atom numbering system shown in Figure 3 and are listed alongside those of ours in Tables 3 and 4. Discrepancies between their assignments and ours can be traced to two sources. First, their C-4 and C-13 assignments are opposite of ours. These ^{13}C assignments likely led to the incorrect assignment of the H-4_{ax}/H-4_{eq} and H-13_{ax}/H-13_{eq} pairs, assuming those assignments were based solely upon C-H correlation experiments. Our C-4/H-4_{ax}/H-4_{eq} assignments were based upon scalar connectivity within the D ring ^1H resonances and Overhauser interactions between H-4_{ax} and H-2_{ax} and between H-4_{ax} and H-6_{ax}. The C-13/H-13_{ax}/H-13_{eq} assignments were confirmed by evidence of a 4J W coupling between H-13_{eq} and H-15_{eq}, and DPGSE-NOE detected Overhauser interactions with H-11_{ax} and H-15_{ax} when H-13_{ax} was selectively irradiated at 1.18 ppm. Second, their H-12_{ax}/H-12_{eq} assignments are opposite of ours. Our assignments were based upon the relative magnitude of the H-12_{ax}/H-12_{eq} – H-11_{ax} COSY cross peaks, one that was large (large anti 3J coupling between H-12_{ax} and H-11_{ax}) and one small (smaller gauche 3J coupling between H-12_{eq} and H-11_{ax}). Our H-12_{ax} assignment was further evidenced by a transannular Overhauser effect between it and H-10_{ax}, detected in a DPGSE-NOE experiment with selective excitation at 3.15 ppm (H-10_{ax}) or at 1.18 ppm (H-12_{ax}).

Table 3. Experimental ^{13}C chemical shifts for **3** from Duddeck et al., this work, and shifts computed at the mPW1W91/6-311+G(2d,p)/PCM(DMSO) level using B3LYP/6-31G(d) geometries. Bold entries indicate shifts not in agreement with values reported here.

^{13}C	$\delta_{\text{exp.}}$ (ppm) <i>Duddeck et al.</i>	$\delta_{\text{exp.}}$ (ppm) <i>This Work</i>	$\delta_{\text{comp.}}$ (ppm) <i>This Work</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc}} $ <i>Duddeck et al.</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc}} $ <i>This Work</i>
2	68.1	68.07	68.50	0.4	0.43
3	19.4	19.41	18.48	0.92	0.93
4	23.6	21.70	20.83	2.77	0.87
5	26.4	26.43	24.11	2.29	2.32
6	71.4	71.41	72.42	1.02	1.01
7	32.4	32.46	33.47	1.07	1.01
8	26.7	26.69	24.80	1.9	1.89
9	30.5	30.51	30.73	0.23	0.22
10	63.8	63.78	61.65	2.15	2.13
11	65.5	65.53	63.42	2.08	2.11
12	28.4	28.49	26.47	1.93	2.02
13	21.6	23.66	21.41	0.19	2.25
14	24.9	24.97	23.27	1.63	1.70
15	54.5	54.57	51.93	2.57	2.64
17	60.4	60.39	58.37	2.03	2.02
18	45.5	45.42	40.26	5.24	5.16

Table 4. Experimental ^1H chemical shifts for **3** from Duddeck et al., this work, and shifts computed at the mPW1W91/6-311+G(2d,p)/PCM(DMSO) level using B3LYP/6-31G(d) geometries. Bold entries indicate shifts not in agreement with values reported here.

^1H	$\delta_{\text{exp.}}$ (ppm) <i>Duddeck et al.</i>	$\delta_{\text{exp.}}$ (ppm, mult ^a) <i>This Work</i>	$\delta_{\text{comp.}}$ (ppm) <i>This Work</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc}} $ <i>Duddeck et al.</i>	$ \delta_{\text{exp.}} - \delta_{\text{calc}} $ <i>This Work</i>
2ax	3.24	3.23 ddd	3.20	0.04	0.03
2eq	3.54	3.52 br d	3.33	0.21	0.19
3ax	1.92	1.93 m	1.98	0.06	0.05
3eq	1.68	1.69 m	1.71	0.03	0.02
4ax	1.17	1.54 ddddd	1.63	0.46	0.09
4eq	1.67	1.71 m	1.84	0.17	0.13
5ax	1.90	1.88 dddd	1.98	0.08	0.10
5eq	1.74	1.74 m	1.71	0.03	0.03
6ax	3.31	3.27 br d	3.56	0.25	0.29
7eq	1.76	1.76 br m	1.71	0.05	0.05
8	1.35	1.34 ddd	1.44	0.09	0.10
8'	2.30	2.29 dddd	2.29	0.01	0
9eq	2.10	2.09 br m	1.98	0.12	0.11
10ax	3.16	3.15 dd	3.27	0.11	0.12
10eq	3.65	3.61 dd	3.33	0.32	0.28
11ax	1.89	1.89 br d	2.07	0.18	0.18
12ax	1.30	1.18 m	1.16	0.14	0.02
12eq	1.19	1.29 m	1.27	0.08	0.02
13ax	1.56	1.18 m	1.21	0.35	0.03
13eq	1.69	1.68 m	1.63	0.06	0.05
14ax	1.45	1.44 ddddd	1.44	0.01	0
14eq	1.52	1.54 br d	1.53	0.01	0.01
15ax	2.05	2.05 ddd	2.19	0.14	0.14
15eq	2.69	2.69 br d	2.67	0.02	0.02
17ax	2.02	2.01 dd	2.19	0.17	0.18
17eq	2.57	2.57 ddd	2.46	0.11	0.11
18	3.12	3.11 s	2.90	0.22	0.21

^aNote: **4** $J(\text{Hz})$: $2_{\text{ax}}, 2_{\text{eq}} = 12.3$, $2_{\text{ax}}, 3_{\text{ax}} = 12.3$, $2_{\text{ax}}, 3_{\text{eq}} = 3.3$, $4_{\text{ax}}, 4_{\text{eq}} = 13.0$, $4_{\text{ax}}, 3_{\text{ax}} = 13.0$, $4_{\text{ax}}, 5_{\text{ax}} = 13.0$, $4_{\text{ax}}, 3_{\text{eq}} = 4.8$, $4_{\text{ax}}, 5_{\text{eq}} = 4.8$, $5_{\text{ax}}, 5_{\text{eq}} = 13.0$, $5_{\text{ax}}, 6_{\text{ax}} = 12.5$, $5_{\text{ax}}, 4_{\text{eq}} = 4.2$, $8, 8' = 14.6$, $8, 9_{\text{eq}} = 2.2$, $8, 7_{\text{eq}} = 2.2$, $8', 7_{\text{eq}} = 4.8$, $8', 9_{\text{eq}} = 4.8$, $8', 17_{\text{eq}} = 2.2$, $10_{\text{ax}}, 10_{\text{eq}} = 13.1$, $10_{\text{ax}}, 9_{\text{eq}} = 3.2$, $10_{\text{eq}}, 9_{\text{eq}} = 10.1$, $11_{\text{ax}}, 12_{\text{ax}} = 10.1$, $14_{\text{ax}}, 14_{\text{eq}} = 12.5$, $14_{\text{ax}}, 13_{\text{ax}} = 12.5$, $14_{\text{ax}}, 15_{\text{ax}} = 12.5$, $14_{\text{ax}}, 13_{\text{eq}} = 3.7$, $14_{\text{ax}}, 15_{\text{eq}} = 3.7$, $15_{\text{ax}}, 15_{\text{eq}} = 11.8$, $15_{\text{ax}}, 14_{\text{eq}} = 2.9$, $17_{\text{ax}}, 17_{\text{eq}} = 11.0$, $17_{\text{ax}}, 7_{\text{eq}} = 2.2$, $17_{\text{eq}}, 7_{\text{eq}} = 2.2$, $17_{\text{eq}}, 8' = 2.2$.

Computational Results

^{13}C and ^1H NMR chemical shift assignments for **4** and **3** were systematically compared with computed values ($|\Delta\delta_{\text{exp}} - \Delta\delta_{\text{calc}}|$ in Tables 1-4).

^{13}C and ^1H Chemical Shift Comparison for Compound 4. We specifically assessed experimental discrepancies in ^{13}C chemical shift assignments at C-2, C-3, C-4 and C-10, and in ^1H chemical shifts at the diastereotopic positions: H-2_{ax}/H-2_{eq}, H-3_{ax}/H-3_{eq}, H-4_{ax}/H-4_{eq}, H-8/H-8', H-10_{ax}/H-10_{eq}, H-12_{ax}/H-12_{eq}, H-15_{ax}/H-15_{eq}, and H-17_{ax}/H-17_{eq}.

For Simeonov and co-workers' ^{13}C assignments, we observe $|\Delta\delta_{\text{exp}} - \Delta\delta_{\text{calc}}|$ of 4.19 ppm at C-2, 3.10 ppm at C-3, 1.38 ppm at C-4, and 3.02 ppm at C-10. In contrast, our assignments resulted in $|\Delta\delta_{\text{exp}} - \Delta\delta_{\text{calc}}|$ of 0.04 ppm at C-2, 0.49 ppm at C-3, 1.26 ppm at C-4, and 1.11 ppm at C-10 ppm. At all four positions, our assignments were in better agreement with predicted values. With regard to the ^1H chemical shifts, the $|\Delta\delta_{\text{exp}} - \Delta\delta_{\text{calc}}|$ for Simeonov and co-workers' assignments ranged from 0.02 to 0.68 ppm, while the greatest deviation for any of our backbone ^1H assignments was 0.25 ppm. The calculated shifts were in qualitative agreement with our relative shielding values assigned for all diastereotopic pairs, with the exception of H-2_{ax}/H-2_{eq}. In contrast, Simeonov and co-workers' chemical shift assignments for the H-3_{ax}/H-3_{eq}, H-4_{ax}/H-4_{eq}, H-8/H-8', H-10_{ax}/H-10_{eq}, H-12_{ax}/H-12_{eq}, H-15_{ax}/H-15_{eq}, and H-17_{ax}/H-17_{eq} pairs were in qualitative disagreement with calculations. Overall, there is an excellent agreement between our ^{13}C and ^1H assignments and the computational results irrespective of the computational level of theory, as indicated by the mean absolute deviation (MAD) values shown in Tables 5 and 6. The reduced percentage difference in ^{13}C MAD values between our assignments and those of Simeonov and co-workers should be viewed in light of the fact that there were discrepancies in only 4 out of 16 ^{13}C chemical shifts. The larger percentage difference in ^1H MAD values is reflective of assignment discrepancies in 16 out of 27 ^1H chemical shift values.

^{13}C and ^1H Chemical Shift Comparison for Compound 3. The ^{13}C assignment/prediction deviations for **3** are generally good, both in terms of absolute and relative values. Regarding the two ^{13}C chemical shifts (C-2 and C-13) assigned differently by our respective groups, the DFT ^{13}C data does not provide much insight, as the shift difference between these sites is ca. 2 ppm. The computed shifts align better with our C-4 assignment and with Duddeck and co-workers' C-13 assignment, which is not surprising when one considers the margin of difference. The DFT ^1H data tends to agree with our assignments, and therefore accurately predicts the shielded character of H-13_{ax} (theory: 1.21 ppm, expt.: 1.18 ppm, Duddeck and co-workers': 1.56 ppm) and the contracted shifts for the H-4_{ax}/H-4_{eq} pair (theory: H-4_{ax} = 1.63 ppm, H-4_{eq} = 1.84 ppm, expt.: H-4_{ax} = 1.54 ppm, H-4_{eq} = 1.71 ppm, Duddeck and co-workers': H-4_{ax} = 1.17 ppm, H-4_{eq} = 1.67 ppm). The DFT ^1H data also supports our relative assignments for the H-12_{ax}/H-12_{eq} pair (theory: H-12_{ax} = 1.16 ppm, H-12_{eq} = 1.27 ppm, expt.: H-12_{ax} = 1.18 ppm, H-12_{eq} = 1.29 ppm, Duddeck and co-workers': H-12_{ax} = 1.30 ppm, H-12_{eq} = 1.19 ppm).

Table 5. Mean absolute deviations (MADs) of experimental ^{13}C chemical shifts for **4** and **3** with respect to computed ^{13}C chemical shifts at various levels of theory.

^{13}C	mPW1PW91/ 6- 311+G(2d,p)	B3LYP/6- 311+G(2d,p)	B3LYP/6- 31G(d,p)	mPW1PW91/6- 31G(d)	B3LYP/6- 31G(d)
4 <i>This work</i>	1.43	1.36	1.20	1.19	1.06
4 <i>Simeonov et al.</i>	1.98	1.88	1.74	1.74	1.68
3 <i>This work</i>	1.79	1.52	1.20	1.70	1.13

Table 6. Mean absolute deviations (MADs) of experimental ^1H chemical shifts for **4** and **3** with respect to computed ^{13}C chemical shifts at various levels of theory.

^1H	mPW1PW91/ 6- 311+G(2d,p)	B3LYP/6- 311+G(2d,p)	B3LYP/6- 31G(d,p)	mPW1PW91/6- 31G(d)	B3LYP/6- 31Gd
4 <i>This work</i>	0.09	0.11	0.13	0.18	0.15
4 <i>Simeonov et al.</i>	0.23	0.23	0.24	0.27	0.27
3 <i>This work</i>	0.09	0.11	0.14	0.20	0.17

Conclusion

The ^1H chemical shifts and coupling constants and ^{13}C NMR chemical shifts of (*N*-methyl)-(-)-(α)-isosparteinium iodide **4** and (*N*-methyl)-(-)-sparteinium iodide **3** have been assigned using a combination of NMR techniques and computational methods.

Experimental

Sample Preparation and Nuclear Magnetic Resonance Experiments

Compounds **3** and **4** were prepared by reacting the appropriate diamine with methyl iodide in acetone.^[14] 15 mg of each compound was dissolved in 0.7 mL of DMSO-*d*₆, transferred to a 5 mm NMR tube, with TMS vapor added to each sample as a reference. NMR data were collected on a Bruker DPX 400 MHz NMR spectrometer equipped with a 5 mm $^1\text{H}/^{13}\text{C}$ Z-gradient probe at a temperature of 25 °C. 1D ^1H NMR experiments were carried out using a 1-s relaxation delay, 9.0 μs 90° pulse, 2100-Hz spectral width, 32 k data points, and 0.25 Hz/point digital resolution. ^1H spectra were analyzed using post-acquisition Gaussian resolution enhancement, using LB = -2 and GB = 0.25. For 1D ^{13}C NMR experiments, which were performed with composite-pulse ^1H decoupling, the acquisition parameters were 2-s relaxation delay, 8 μs 90° pulse, 23980 Hz spectral

width, 64 k data points, and 0.37 Hz/point digital resolution. ^{13}C data was processed with 1 Hz exponential line broadening. Gradient-enhanced 2D COSY,^[23-24] gradient-enhanced 2D ^1H - ^{13}C edited HSQC,^[25] 2D ROESY,^[26] 2D TOCSY,^[27] 1D TOCSY,^[28] and 1D DPGFSE NOE^[29] experiments were also utilized. A full description of acquisition and processing parameters for these experiments is provided in the Supporting Information.

Computational Methodology

The methodology for computing NMR parameters was based upon similar work in the literature.^[18] Crystal structures for **3**^[11] and **4**^[13] were retrieved from the Cambridge Crystallographic Database and the cationic skeletons were used as starting structures for calculations. A 3-step process was utilized to arrive at the computed shifts. Initially, the lowest-energy conformer was identified through 10,000 steps of a Monte Carlo multiple minimum (MCMM) algorithm with the OPLS3 force field in Maestro.^[30-33] The lowest energy conformers for **3** and **4** corresponded well with the X-ray structures. All of the higher-energy conformers had energy differences of more than 5 kcal/mol, leading us to discard those structures and solely focus on the lowest-energy conformer for the remaining two steps of the analysis. Next, the minimum-energy structures for each compound were optimized using the B3LYP/6-31G(d) level of theory in Gaussian 09.^[34] Subsequently, the NMR chemical shifts were computed with the GIAO option using the mPW1PW91 method with a polarizable continuum model (PCM) for DMSO.^[35-37] These calculations were done with a variety of different basis sets, as shown in the Supporting Information. In regards to the basis sets, we noticed that modest basis sets yielded slightly better results for carbon chemical shifts for both compounds. This trend has been previously observed in the literature.^[18] We also utilized the B3LYP method with PCM for DMSO to further test the merits of the chemical shift assignments. The MSTD approach, set forth by Sarotti and Pellegrinet, was utilized by using methanol as the computational reference for the ^{13}C shielding calculations.^[38] Tetramethylsilane was utilized as the ^1H shielding reference compound. The $J_{\text{H-H}}$ coupling constants were calculated with B3LYP/6-31G(d,p) with PCM for DMSO level of theory.^[39-40] In order to accurately approximate the Fermi contact terms that dominate $J_{\text{H-H}}$ values, we invoked the ‘mixed’ basis set option in Gaussian 09 in order to uncontract and augment the core basis sets.^{[40][49]} All of the quantum-mechanical treatments were done in Gaussian 09. Simulation of ^1H NMR spectra was done with the NUMARIT algorithm^[41] in SpinWorks.^[42] 3D molecular models of optimized structures were generated with PyMOL.^[43]

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

^1H and ^{13}C assignment narratives, acquisition and processing parameters for 2D and 1D selective excitation experiments, experimental NMR results, simulated NMR spectra, computational protocols, calculated NMR chemical shifts, and computed ^1H - ^1H J coupling constants.

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