Analytical Methods

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Observation of Diastereotopic Signals in ^{15}N NMR Spectroscopy**

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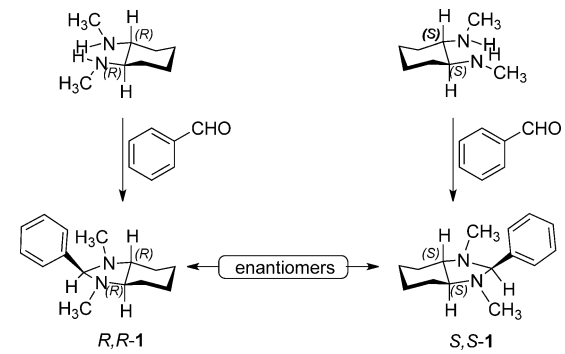
Abstract: *The first example in the literature of a compound showing anisochronous ^{15}N atoms resulting from diastereotopicity is described. Racemic 1,3-dimethyl-2-phenyloctahydro-1H-benzimidazole was prepared and studied by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. If convenient conditions were used (monitored by theoretical calculations of $^{2}J_{N\text{-}H}$ spin–spin coupling constants), two ^{15}N NMR signals were observed and corresponded to the diastereotopic atoms. GIAO/density-functional calculations of chemical shifts were not only in good agreement with the experimental values but also served as prediction tools. This study suggests that ^{15}N NMR spectroscopy could be used to probe chirality.*

Diastereotopic protons, usually belonging to methylene groups, have fascinated NMR users for a long time (1957).[1] The observation of chemical-shift nonequivalence (anisochronism) for identical geminal nuclei attached to a tetrahedral center is a well-known phenomenon in NMR spectroscopy. The origin of the anisochronism and the recognition that in conformationally mobile systems there are two terms, one intrinsic and one depending on the conformer population, has been known for a long time,[2] and it is reported in several books.[3] The concept was extended to other nuclei, and actually, the observation for ^{19}F was also reported in 1957,[4] and those for ^{13}C and ^{31}P were published respectively in 1973[5] and 1974.[6] Anisochronism for ^{2}H was published in 1983,[7] for ^{3}H in 2005,[8] for ^{7}Li in 2014,[9] and for ^{17}O in 1990.[10] Obviously, besides ^{1}H, the most reported examples concern ^{13}C,[11] ^{19}F,[12] and ^{31}P.[13]

Realizing that there was no example of observation of anisochronous ^{15}N chemical shifts of diastereotopic nitrogen atoms, we decided to fill this gap. We selected molecules having two N atoms in a geminal arrangement and molecules which were synthetically accessible (i.e., octahydro-1*H*-benzo[d]imidazole derivatives; see Table S1 in the Supporting Information). We calculated their chemical shifts using a combination of GIAO/B3LYP/6-311++G(d,p) calculations of absolute shieldings with the Gaussian 09 software,[14] and robust empirical equations to transform these absolute shieldings into chemical shifts.[15] The compound **1** (Scheme 1) was chosen as a representative example among the studied molecules. The compound **1**, not previously reported, was synthesized as a mixture of both enantiomers, *rac*-**1**, using a method similar to that reported for other aryl groups.[16] Starting from racemic trans-*N*,*N*′-dimethylcyclohexane-1,2-diamine and benzaldehyde we obtained the desired compound, 1,3-dimethyl-2-phenyloctahydro-1*H*-benzimidazole, *rac*-**1**, for which calculated and experimental chemical shifts are reported in Figure 1.



Scheme 1. Synthesis of *rac*-**1**. Reagents and conditions: *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (1 equiv), benzaldehyde (1 equiv), toluene, 4 Å molecular sieves, 120 °C, 22 h (15 %).

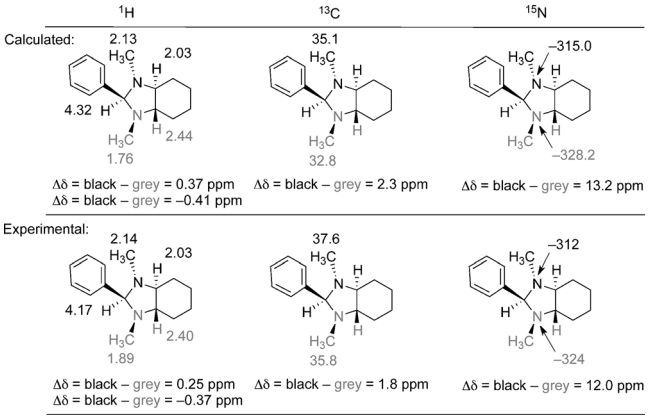


Figure 1. Calculated and experimental ^{1}H, ^{13}C, and ^{15}N chemical shifts.

The ^{1}H and ^{13}C chemical shifts were in excellent agreement with the calculated values (Figure 1) but the ^{15}N NMR spectrum (obtained by g-HMBC experiment using the standard J value of 8 Hz) showed one big signal at $\delta = -324$ ppm with its corresponding cross-peaks ($\delta = 4.17$ and 1.89 ppm; Figure S5) and a very small signal at $\delta = -312$ ppm with concomitant small cross-peaks ($\delta = 4.17$ and 2.14 ppm).

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Since the experimental $\Delta\delta$ values were similar to those predicted by the calculations, the difference in intensity between both ^{15}N NMR peaks was unexpected. As we suspected, the J value used in the g-HMBC experiment was not a convenient one, and we calculated the ^{2}J (^{15}N-^{1}H) coupling constants of **1** at the B3LYP/6-311++G(d,p) level of theory (Figure 2).

As can be seen in Figure 2, the only spin–spin coupling constant (SSCC) $>|1|$ Hz is that between the 2-H and the "grey" nitrogen atom, and would thus explain the difference in intensity observed between both geminal ^{15}N signals in the g-HMBC experiment optimized for $J = 8$ Hz. Consequently, we repeated the g-HMBC experiments using J values of 2 Hz and 6 Hz (Figure 3). With $J = 6$ Hz, both ^{15}N signals were still very different in intensity whereas with $J = 2$ Hz, the signal for the grey ^{15}N at $\delta = -324$ ppm and the black ^{15}N at $\delta = -312$ ppm were of rather similar intensities.

In conclusion, by using theoretical calculations as a predictive tool we have been able to find the first example of a compound showing anisochronous ^{15}N atoms resulting from diastereotopicity. This study shows that GIAO/density-functional calculations are a powerful tool to predict chemical shifts and coupling constants and can help in the elucidation of ambiguous NMR spectra of organic molecules.

In Figure 4 we have summarized some calculations to show the generality of the idea. The compound **2** is related to organocatalysts reported by Alexakis,[17] the compound **3** is a tris-arylmethane propeller, the compound **4** is related to DABN, and the compound **5** is a derivative of [5]helicene. The $\Delta\delta$ values in Figure 4 correspond to minimum-energy conformations (two in the case of **2**) and include intrinsic and conformational origins (see the Supporting Information). Several examples, for instance **4** and **5**, show that ^{15}N NMR spectroscopy could be used as a probe for chirality.[3a,18]

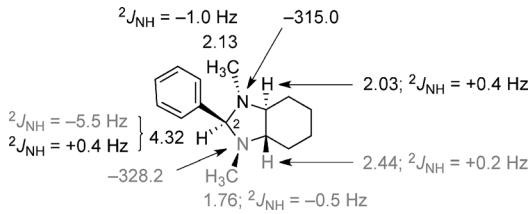

Figure 2. Calculated $^{2}J_{NH}$ coupling constants.

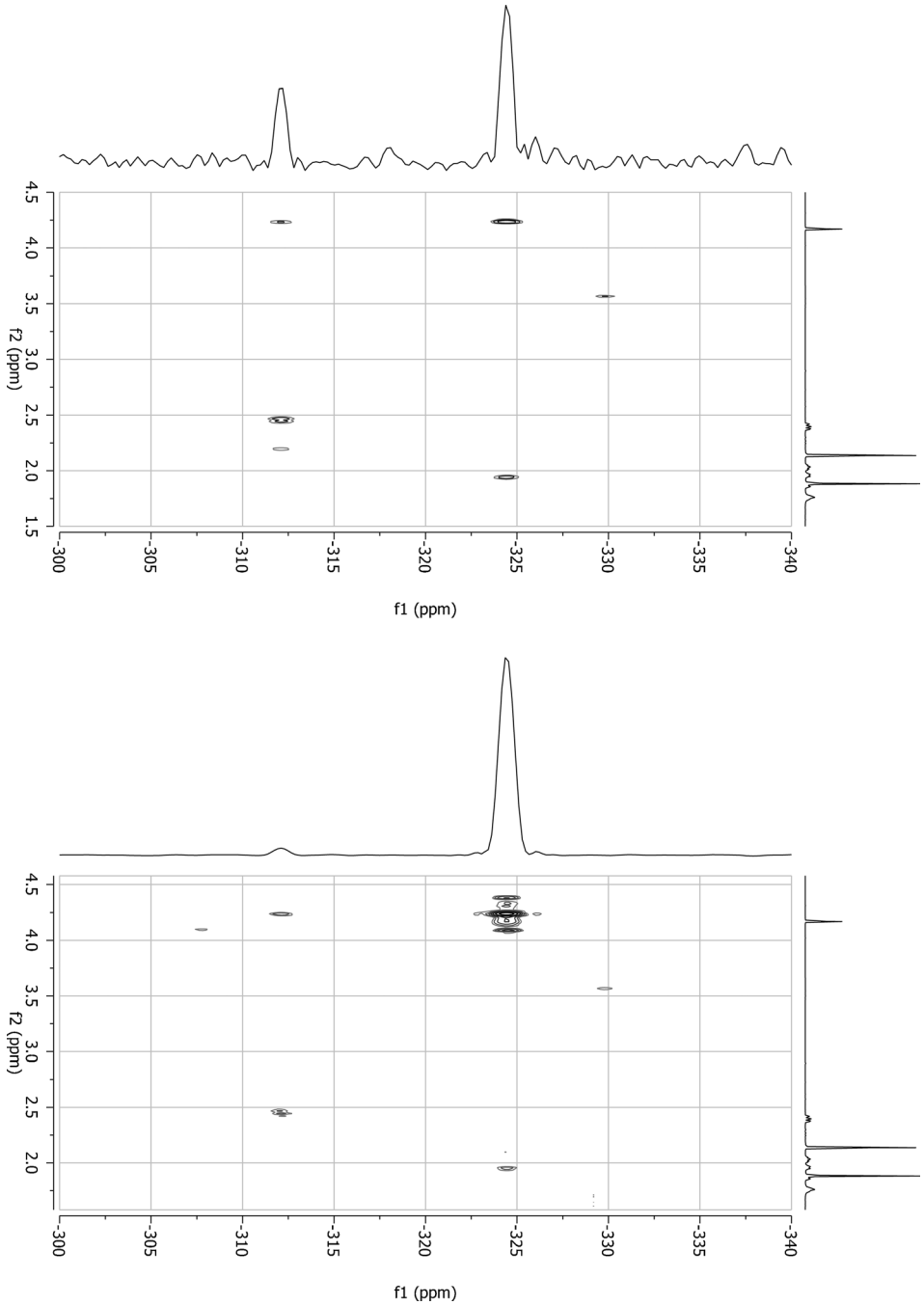

Figure 3. g-HMBC ^{15}N spectra of *rac*-**1** optimized for J values of 2 Hz (top) and 6 Hz (bottom).

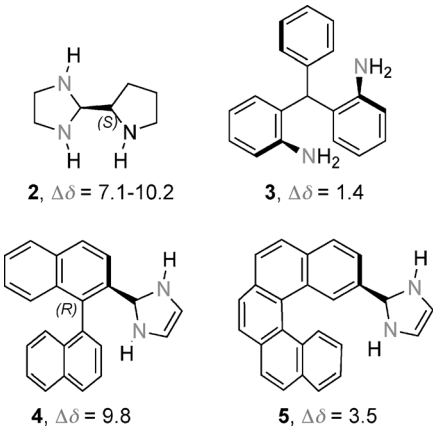

Figure 4. Calculated [B3LYP/6-311++G(d,p)] ^{15}N anisochronies (ppm).

Experimental Section

Synthesis of 1,3-dimethyl-2-phenyloctahydro-1*H*-benzimidazole (*rac*-**1**). A sealed tube charged with a mixture of trans-*N*,*N*′-dimethylcyclohexane-1,2-diamine (198 mg, 1.39 mmol), benzaldehyde (142 μL, 1.39 mmol), and 4 Å molecular sieves in anhydrous toluene (2 mL) was heated at 120 °C for 22 h under an argon atmosphere. The reaction mixture was filtered on celite and the filter cake was rinsed with CH_2Cl_2. The filtrate was evaporated under vacuum to give a brown oil. Gravity silica chromatography with Isolute (5 g) prepacked column eluting with hexanes/EtOAc (100:0→50:50) yielded the product as a brown oil (49 mg, 15 %). HPLC (UV) > 95 %. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.35$–7.30 (m, 2H), 7.26 (ddt, $J = 7.6$, 6.2, 1.2 Hz, 2H), 7.24–7.19 (m, 1H), 4.17 (s, 1H), 2.40 (ddd, $J = 10.7$, 9.0, 3.5 Hz, 1H), 2.14 (d, $J = 0.7$ Hz, 3H), 2.03 (ddd, $J = 10.3$, 9.0, 3.7 Hz, 1H), 1.99–1.92 (m, 1H), 1.89 (d, $J = 0.7$ Hz, 3H), 1.87–1.84 (m, 1H), 1.80–1.72 (m, 2H), 1.29–1.11 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 140.0$, 129.5, 128.1, 128.0, 89.9, 69.5, 68.6, 37.6, 35.8, 29.1, 29.1, 24.6, 24.5 ppm. ^{15}N NMR (51 MHz, $CDCl_3$): $\delta = -324$, -312 ppm. HRMS (ESI^+) *m*/*z* 230.1786 ($C_{15}H_{22}N_2$ requires 230.1783).

NMR spectra were recorded at 298 K, using $CDCl_3$ as solvent, on a Varian SYSTEM 500 NMR spectrometer equipped with a 5 mm HCN cold probe, operating at 499.81 (^{1}H), 125.69 (^{13}C), and 50.65 MHz (^{15}N). ^{1}H and ^{13}C chemical shifts are reported in ppm from Me_4Si and ^{15}N chemical shifts from $MeNO_2$. ^{1}H- and ^{13}C NMR recordings were performed using standard Varian pulse sequences. 2D (^{1}H-^{15}N) NMR gradient heteronuclear multiple-bond correlation (g-HMBC) experiments were obtained with a ^{1}H spectral window of 5924 Hz, a ^{15}N spectral window of 9625 Hz, 1 s of relaxation delay, 1024 data points, and 200 time increments, 64 transients per increment, with a linear prediction to 512. The data were zero-filled to 1024 × 1024 real points. As the intensity of cross peaks depends on the heteronuclear long-range coupling constant, two experiments were obtained one optimized for 6 Hz and the second optimized for 2 Hz.

Keywords: analytical methods · chirality · density functional calculations · nitrogen heterocycles · NMR spectroscopy

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