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Hydrogen Bonds

The Largest ^{15}N–^{15}N Coupling Constant Across an NHN Hydrogen Bond**

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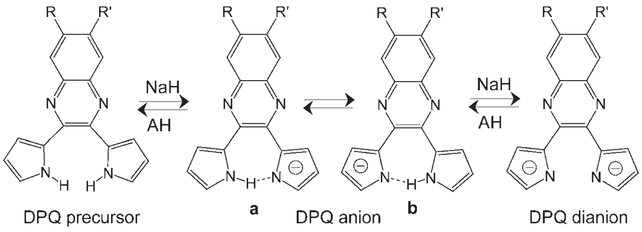
Since the discovery of NMR coupling constants across hydrogen bonds A–H···B containing nuclei with spin $^1/_2$, such as A, B = ^{19}F, ^{15}N,[1–3] it has been established that these NMR parameters can not only be used to detect hydrogen bridges in biomolecules[4] but also to determine the geometries of strong hydrogen bonds in solution.[5] It has been shown experimentally and by ab initio calculations[1] that scalar two-bond coupling constants $^2J_{AB}$ attain maximum values when the A···B distances are at a minimum. Whereas the maximum values have been established for FHF and NHF hydrogen bonds, the corresponding maxima are still unknown in the case of NHN bridges. To date, only $^2J_{^{15}N^{15}N}$ values less than 11 Hz have been detected in nucleic acid base pairs,[3] protonated sponges,[6,7] and six-[8] and seven-membered[9] H-chelates. In contrast, DFT calculations gave maximum coupling constants $^2J_{NN} = 25$ Hz,[5d] corresponding to the shortest possible N···N distance of about 2.5 Å.[10] More reliable high-level coupled-cluster EOM calculations of small model systems predicted even larger coupling constants.[11,12]

Herein we describe a novel class of anionic H-chelates with ^{15}N–^{15}N coupling constants of more than 16 Hz. These anions were obtained by deprotonation of 2,3-dipyrrol-2-ylquinoxalines (DPQs, Scheme 1). DPQs have been synthesized and studied as colorimetric anion receptors for charge-dense species, such as fluoride.[13] However, their unusual geometry makes it likely that their monodeprotonated forms would have unusually short NHN hydrogen bonds and thus unusually large ^{15}N–^{15}N coupling constants. This expectation has been realized, and we present herein the results of various NMR spectroscopy experiments and ab initio DFT calculations that characterize the geometries of the intramolecular NHN hydrogen bonds of these anions.



1: R = H, R' = H   **2**: R = H, R' = NO_2 **3**: R = R' = NO_2

Scheme 1. Chemical structures of substituted 2,3-dipyrrol-2-ylquinoxalines (DPQ) and their deprotonated mono- and dianions. **1**: 2,3-dipyrrol-2-ylquinoxaline, **2**: 6-nitro-2,3-dipyrrol-2-ylquinoxaline, **3**: 6,7-dinitro-2,3-dipyrrol-2-ylquinoxaline. The monoanions are subject to a fast proton tautomerism between two forms labeled as **a** and **b**. AH = trifluoroacetic acid.

The NHN anions of the DPQs **1–3** were generated by treatment of solutions of the DPQ precursors in 5:1 CD_2Cl_2/[D$_6$]DMSO mixtures to which small amounts of solid NaH were added. Minute quantities of dihydrogen were produced, along with the corresponding monoanion as the major organic product (see Experimental Section). [D$_6$]DMSO was added to solvate the Na^+ counterions, while CD_2Cl_2 was used as the primary solvent because it provided the reduced viscosity needed to carry out various NMR spectroscopic analyses at lower temperatures (conditions under which proton exchange was found to be slow).

Figure 1a shows the signals of the pyrrolic protons, labeled H1 and H17, of [$^{15}N_2$]**2** recorded at 233 K in CD_2Cl_2/[D$_6$]DMSO. Under these conditions, two signals are observed, namely at 11.81 and 11.93 ppm. Each signal is split into a doublet, with coupling constants $^1J_{^{15}N^1H} = -97.6$ and -97.7 Hz,

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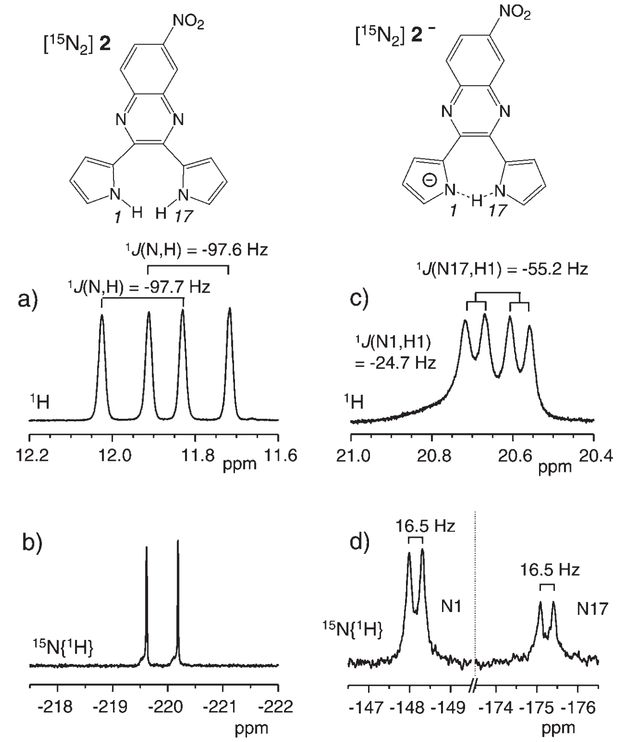

Figure 1. Partial ^1H and ^{15}N NMR spectra of $[^{15}N_2]$**2** and its anion $[^{15}N_2]$**2**$^-$ dissolved in a mixture of CD_2Cl_2/[D_6]DMSO (5:1): a) ^1H signals of H1 and H17 of **2** at 233 K; b) $^{15}N\{^1H\}$ spectrum of $[^{15}N_2]$**2** at 233 K; c) ^1H signal of $[^{15}N_2]$**2**$^-$ at 193 K, and d) $^{15}N\{^1H\}$ spectrum of $[^{15}N_2]$**2**$^-$ at 193 K.

respectively. These values are in accord with those recorded for pyrroles[14] and porphyrins.[15] The corresponding $^{15}N\{^1H\}$ NMR spectrum (Figure 1b) has two lines for the two pyrrole nitrogen atoms of $[^{15}N_2]$**2**. No scalar coupling between the two ^{15}N nuclei is observed, a finding that is consistent with the absence of intramolecular NHN hydrogen bonds.

In contrast, a single pyrrolic proton signal at 20.65 ppm is observed at 193 K for the monoanion $[^{15}N_2]$**2**$^-$ (Figure 1c). This signal is split into a pair of doublets, with values of $J_{N17H17} = -55.2$ and $J_{N1H1} = -24.7$ Hz. Unfortunately, we could not establish clearly whether these values are intrinsic or arise from a fast nondegenerate proton tautomerism between two tautomers **a** and **b** according to Scheme 1. We favor the latter possibility, as the values change slightly with temperature.[16] The assignment of the coupling constants is tentative, and based on the assumption that $[^{15}N_2]$**2b**$^-$ is energetically favored as corroborated by the DFT calculations described below. The average of both couplings is −40 Hz, and the same value is observed for the symmetrical anion **3**$^-$ in [D_6]DMSO at 298 K and natural ^{15}N abundance. Values of $|-40|$ Hz or less have been predicted for short symmetrical NHN bonds.[3,5d]

The corresponding $^{15}N\{^1H\}$ NMR spectrum is depicted in Figure 1d. Again, two signals are observed. We ascribe the upfield signal to N17 and the downfield signal to N1. Their signal intensities are not equal as they experience different nuclear Overhauser effects.[17] However, both signals appear as doublets, each with a coupling constant of $J_{NN} = 16.5$ Hz; this is the largest value recorded to date.

To characterize further the hydrogen bonds of the mono-deprotonated DPQ anions derived from **1**–**3**, we studied the effect of D-for-H isotope exchange on their respective NMR chemical shifts. Selected results are reproduced in Figure 2;

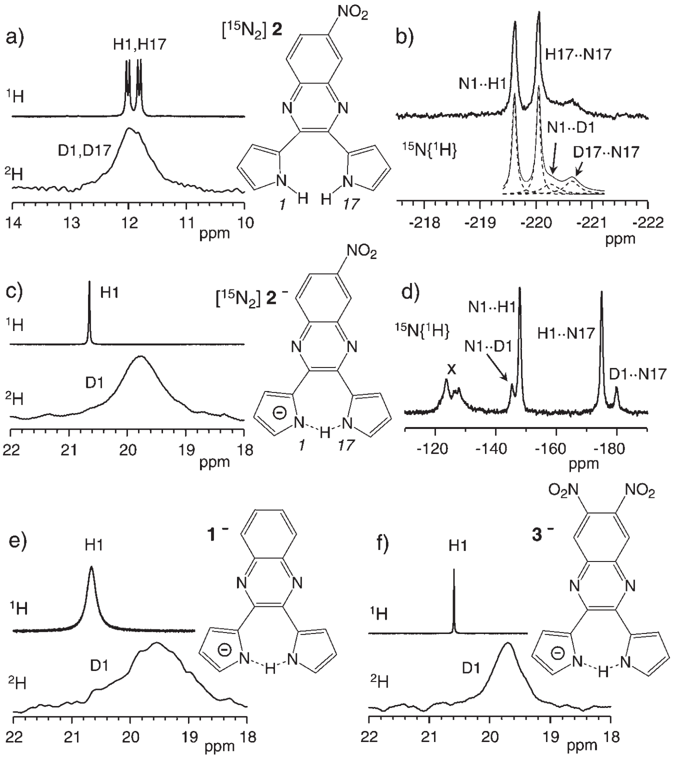

Figure 2. a) Partial ^1H and ^2H and b) $^{15}N\{^1H\}$ NMR spectra of a 0.02 M solution of $[^{15}N_2]$**2** in a mixture of CD_2Cl_2/[D_6]DMSO (10:1) recorded at 233 K with a deuterium fraction $x_D \approx 0.3$ in the labile (pyrrolic NH) proton sites. c) Partial ^1H and ^2H NMR spectra of the anion $[^{15}N_2]$**2**$^-$ obtained in a mixture of CD_2Cl_2/[D_6]DMSO (5:1) after addition of solid NaH at 233 K. d) $^{15}N\{^1H\}$ NMR spectra of $[^{15}N_2]$**2** recorded at 193 K and at $x_D \approx 0.3$; otherwise, the conditions were the same as in (c). The signals labeled as **x** arise from the dianion $[^{15}N_2]$**2**$^{2-}$. e,f) Partial ^1H and ^2H NMR spectra of 0.02 M solutions of **1**$^-$ and **3**$^-$ in a mixture of CD_2Cl_2/[D_6]DMSO (5:1) recorded at 233 K with a deuterium fraction $x_D \approx 0.3$ in the mobile proton sites.

the deuteron lines are broadened by the usual quadrupole relaxation. In the case of the neutral species $[^{15}N_2]$**2**, deuterium exchange produces only a small primary shift $\delta(NDN)-\delta(NHN)$ with respect to the original proton-containing material (Figure 2a). In contrast, a large upfield shift of −0.86 ppm is seen (Figure 2c) when the anion $[^{15}N_2]$**2**$^-$ is deuterated.

Similarly, only a small upfield shift $\delta(NDN)-\delta(NHN) = -0.6$ ppm is found for the two nitrogen atoms of the parent compound $[^{15}N_2]$**2** (Figure 2b). In contrast, in the case of $[^{15}N_2]$**2**$^-$, deuteration shifts the signal of N17 upfield by −5 ppm and the signal of N1 downfield by +2.5 ppm (Figure 2d). As has been shown previously,[18] these isotope effects correspond roughly to a distance sum $r_{NH}+r_{HN} \cong r_{NN}$ on the order of 2.6 Å.

The results presented in Figure 2 e and f provide support for the notion that the anions $\mathbf{1}^-$ and $\mathbf{3}^-$, although symmetrical, are otherwise analogous to $\mathbf{2}^-$. The ^{1}H chemical shifts, $\delta = 20.66$ and 20.59 ppm, shift by -1.13 and -0.88 ppm, respectively, (i.e., upfield) after deuteration. Given this consistent and expected behavior, we did not synthesize and study the ^{15}N isotopologues of these anions. To corroborate the estimated hydrogen-bond distances, we calculated the equilibrium geometries of all the anions using DFT ab initio methods. The results are shown in Table 1. The distances are in the expected range, although a comparison with experimental values would require corrections for anharmonic zero-point vibrations. The energy of the tautomer $\mathbf{2a}^-$ was calculated to be about 5.9 kJ mol^{-1} larger than of $\mathbf{2b}^-$, a difference that supports the above-mentioned assignments for the ^{15}N chemical shifts and the associated coupling constants J_{NH}.

Table 1: Equilibrium hydrogen-bond geometries of $\mathbf{1}^-$, $\mathbf{2}^-$, and $\mathbf{3}^-$ calculated using DFT at the B3PW91/6-31 + G** level.

Anion	r_{NN} [Å]	r_{N-H} [Å]	$r_{H\cdots N}$ [Å]	N−H···N Angle [°]
$\mathbf{1}^-$	2.543	1.100	1.489	158.0
$\mathbf{2a}^-$	2.524	1.117	1.452	158.4
$\mathbf{2b}^-$	2.562	1.082	1.533	156.8
$\mathbf{3}^-$	2.554	1.087	1.518	156.9

Several interesting questions arise. One of these is why the values of J_{NN} of the DPQ anions are much larger than those of the related proton sponges.[6,7] Possible explanations are the differences in the overall charge of the systems, the hybridization of the nitrogen atoms, and the specific nature of the intermolecular interactions. Although further study is required, we do not think charge effects are dominant, as the chemical shifts of the hydrogen-bonded protons in both types of compounds are similar.

A second question is why the experimental values of J_{NN} for strong NHN hydrogen bonds are generally smaller than those expected from ab initio calculations. We believe that this result could reflect the observation[18] that the heavy-atom distances of the strongest and shortest hydrogen bonds are larger than those of the calculated equilibrium structures. This disparity arises from the space required by the hydrogen-bond proton for quantum zero-point vibrations,[19] an effect that leads eventually to a reduction in the J_{NN} value.

In conclusion, we have shown that deprotonation of 2,3-dipyrrol-2-ylquinoxalines leads to hydrogen-bonded anions exhibiting the largest ^{15}N–^{15}N coupling constants observed to date. However, further efforts will be needed to quantify the relation between various observable NMR parameters and the geometries of strong NHN hydrogen-bonded systems.

Experimental Section

The NMR measurements were performed on a Bruker AMX 500 spectrometer operating at 500.13 MHz for ^{1}H. The ^{15}N spectra were measured using the standard pulse sequences, and using liquid CH_3NO_2 as reference, a species that resonates at 341.17 ppm relative to solid $^{15}NH_4Cl$.[20]

The synthesis of the DPQs was performed according to procedures described previously.[21,22] Doubly ^{15}N-labeled analogues were prepared in a similar manner, starting from ^{15}N-labeled pyrrole, which was enriched to about 95 % with ^{15}N.

The deprotonated DPQ anions were generated in the NMR tubes used for analysis by adding small amounts of solid NaH to 0.01–0.02 M DPQ solutions in CD_2Cl_2/[D$_6$]DMSO (5:1). The formation of the anions was monitored by ^{1}H NMR spectroscopy. The dianion $\mathbf{2}^{2-}$ could be observed in the presence of an excess of NaH, which was converted back into $\mathbf{2}^-$ (monitored by NMR spectroscopy) by adding trifluoroacetic acid. Deuteration of the exchangeable proton sites was achieved by dissolving the compounds in dichloromethane/[D$_1$]methanol.

Ab initio calculations were performed using the Gaussian 98 set of programs[23] at the B3PW91/6-31 + G** level of density functional theory (DFT).[24]

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[1] I. G. Shenderovich, S. N. Smirnov, G. S. Denisov, V. A. Gindin, N. S. Golubev, A. Dunger, R. Reibke, S. Kirpekar, O. L. Malkina, H. H. Limbach, *Ber. Bunsen-Ges.* **1998**, *102*, 422 – 428.

[2] a) A. J. Dingley, S. Grzesiek, *J. Am. Chem. Soc.* **1998**, *120*, 8293 – 8297; b) A. J. Dingley, J. E. Masse, R. D. Peterson, M. Barfield, J. Feigon, S. Grzesiek, *J. Am. Chem. Soc.* **1999**, *121*, 6019 – 6027; c) F. Cordier, S. Grzesiek, *J. Am. Chem. Soc.* **1999**, *121*, 1601 – 1602; d) F. Cordier, M. Rogowski, S. Grzesiek, A. Bax, *J. Magn. Reson.* **1999**, *140*, 510 – 512; e) K. Pervushin, A. Ono, C. Fernández, T. Szyperski, M. Kainosho, K. Wüthrich, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 14147 – 14151.

[3] M. Barfield, A. J. Dingley, J. Feigon, S. Grzesiek, *J. Am. Chem. Soc.* **2001**, *123*, 4014 – 4022.

[4] S. Grzesiek, F. Cordier, V. Jaravine, M. Barfield, *Prog. Nucl. Magn. Reson. Spectrosc.* **2004**, *45*, 275 – 300.

[5] a) N. S. Golubev, I. G. Shenderovich, S. N. Smirnov, G. S. Denisov, H. H. Limbach, *Chem. Eur. J.* **1999**, *5*, 492 – 497; b) I. G. Shenderovich, A. P. Burtsev, G. S. Denisov, N. S. Golubev, H. H. Limbach, *Magn. Reson. Chem.* **2001**, *39*, S91 – S99; c) I. G. Shenderovich, P. Tolstoy, N. S. Golubev, S. N. Smirnov, G. S. Denisov, H. H. Limbach, *J. Am. Chem. Soc.* **2003**, *125*, 11710 – 11720; d) H. Benedict, I. G. Shenderovich, O. L. Malkina, V. G. Malkin, G. S. Denisov, N. S. Golubev, H. H. Limbach, *J. Am. Chem. Soc.* **2000**, *122*, 1979 – 1988.

[6] M. Pietrzak, J. Wehling, H. H. Limbach, N. S. Golubev, C. López, R. M. Claramunt, J. Elguero, *J. Am. Chem. Soc.* **2001**, *123*, 4338 – 4339.

[7] G. C. Lloyd-Jones, J. N. Harvey, P. Hodgson, M. Murray, R. L. Woodward, *Chem. Eur. J.* **2003**, *9*, 4523 – 4535.

[8] M. Pietrzak, C. Benedict, H. Gehring, E. Daltrozzo, H. H. Limbach, *J. Mol. Struct.* **2007**, *844–845*, 222 – 231.

[9] M. Pietrzak, H. H. Limbach, M. Pérez-Torralba, D. Sanz, R. M. Claramunt, J. Elguero, *Magn. Reson. Chem.* **2001**, *39*, S100 – S108.

[10] H. Benedict, H. H. Limbach, M. Wehlan, W. P. Fehlhammer, N. S. Golubev, R. Janoschek, *J. Am. Chem. Soc.* **1998**, *120*, 2939 – 2950.

[11] a) J. E. Del Bene, S. A. Perera, R. J. Bartlett, *J. Am. Chem. Soc.* **2000**, *122*, 3560 – 3561; b) J. E. Del Bene, M. J. T. Jordan, *J. Am. Chem. Soc.* **2000**, *122*, 4794 – 4797; c) J. E. Del Bene, R. J. Bartlett, *J. Am. Chem. Soc.* **2000**, *122*, 10480 – 10481; d) S. A.

Perera, R. J. Bartlett, *J. Am. Chem. Soc.* **2000**, *122*, 1231–1232; e) J. E. Del Bene, S. A. Perera, R. J. Bartlett, *Magn. Reson. Chem.* **2001**, *39*, S109–S114.

[12] J. E. Del Bene, J. Elguero, *J. Phys. Chem. A* **2006**, *110*, 7496–7502.

[13] a) C. B. Black, B. Andrioletti, A. C. Try, C. Ruiperez, J. L. Sessler, *J. Am. Chem. Soc.* **1999**, *121*, 10438–10439; b) J. L. Sessler, G. D. Pantos, E. Katayev, V. M. Lynch, *Org. Lett.* **2003**, *5*, 4141–4144; c) J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch, H. Furuta, *J. Am. Chem. Soc.* **2002**, *124*, 13474–13479; d) J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch, H. Furuta, *Chem. Commun.* **2002**, 862–863.

[14] G. J. Martin, M. L. Martin, J. P. Gouesnard *^{15}N-NMR Spectroscopy*, Springer, Berlin, **1981**, p. 220.

[15] M. Schlabach, H. Rumpel, H. H. Limbach, *Angew. Chem.* **1989**, *101*, 84–87; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 76–79.

[16] The increase in solvent viscosity at lower temperatures and increased proton exchange at higher temperatures cause line broadening, which makes the determination of coupling constants difficult. At 233 K, for a sample prepared using tetrabutylammonium fluoride, we obtained values of −54.5 and −26 Hz.

[17] J. Hennig, H. H. Limbach, *J. Am. Chem. Soc.* **1984**, *106*, 292–298.

[18] a) H. H. Limbach, M. Pietrzak, H. Benedict, P. M. Tolstoy, N. S. Golubev, G. S. Denisov, *J. Mol. Struct.* **2004**, *706*, 115–119; b) H. H. Limbach, M. Pietrzak, S. Sharif, P. M. Tolstoy, I. G. Shenderovich, S. N. Smirnov, N. S. Golubev, G. S. Denisov, *Chem. Eur. J.* **2004**, *10*, 5195–5204.

[19] Hydrogen-bond isotope effects studied by NMR spectroscopy: H. H. Limbach, G. S. Denisov, N. S. Golubev in *Isotope Effects In Chemistry and Biology* (Eds.: A. Kohen, H. H. Limbach), Taylor & Francis, Boca Raton, FL, **2005**, chap. 7, pp. 193–230.

[20] S. Hayashi, K. Hayamizu, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 688–690.

[21] a) B. Oddo, *Gazz. Chim. Ital.* **1911**, *41*, 248–255; b) D. Behr, S. Brandänge, B. Lindström, *Acta Chem. Scand.* **1973**, *27*, 2411–2414.

[22] J. L. Sessler, C. B. Black, B. Andrioletti, A. C. Try, US Patent 6,482,949, **2002**.

[23] M. J. Frisch, et al. *Gaussian 98*, Revision A7; Gaussian Inc., Pittsburgh, PA, **1998**. For the full reference see the Supporting Information.

[24] a) R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, **1989**; b) N. H. March, *Electron Density Theory of Atoms and Molecules*, Academic Press, San Diego, CA, **1992**.