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Supplementary Material

NMR Chemical Shift and Methylation of 4-Nitroimidazole: Experiment and Theory

Frederick Backler,[A] Marc Antoine Sani,[B] Frances Separovic,[B] Vladislav Vasilyev,[C] and Feng Wang[A,D]

[A]Department of Chemistry and Biotechnology and Centre for Translational Atomaterials, Faculty of Science, Engineering and Technology, Swinburne University of Technology, Hawthorn, Vic. 3122, Australia.

[B]School of Chemistry, Bio21 Institute, University of Melbourne, Melbourne, Vic. 3010, Australia.

[C]National Computational Infrastructure, Australian National University, Canberra, ACT 0200, Australia.

[D]Corresponding author. Email: fwang@swin.edu.au

Table S1 Summary of Natural Population Analysis of 4-NI*

Atom No	Natural Charge	Core	Valence	Rydberg	Total
C 1	0.20445	1.99940	3.76238	0.03377	5.79555
N 2	-0.52322	1.99939	5.51077	0.01306	7.52322
C 3	-0.03152	1.99911	4.00869	0.02372	6.03152
C 4	0.19001	1.99886	3.77911	0.03202	5.80999
N 5	-0.44335	1.99937	5.42329	0.02069	7.44335
H 6	0.24334	0.00000	0.75462	0.00204	0.75666
N 7	0.47621	1.99942	4.46689	0.05748	6.52379
O 8	-0.39923	1.99980	6.38485	0.01458	8.39923
O 9	-0.34177	1.99979	6.32633	0.01565	8.34177
H 10	0.20427	0.00000	0.79402	0.00171	0.79573
H 11	0.42081	0.00000	0.57683	0.00236	0.57919
Total	0.00000	15.99514	41.78778	0.21708	58.00000

4-NI Natural Population

Core	15.99514 (99.9696% of 16)
Valence	41.78778 (99.4947% of 42)

*B3PW91/6-311++g(d,p), gas phase.

Table S2 Summary of Natural Population Analysis of 4-NI in DMSO solvent*

Atom No	Natural Charge	Core	Valence	Rydberg	Total
C 1	0.22440	1.99940	3.74309	0.03312	5.77560
N 2	-0.49978	1.99938	5.48729	0.01311	7.49978
C 3	0.00523	1.99913	3.97313	0.02251	5.99477
C 4	0.17624	1.99890	3.79384	0.03102	5.82376
N 5	-0.49407	1.99939	5.47315	0.02152	7.49407
H 6	0.25539	0.00000	0.74284	0.00177	0.74461
N 7	0.48193	1.99940	4.46283	0.05584	6.51807
O 8	-0.42228	1.99980	6.40773	0.01475	8.42228
O 9	-0.39981	1.99979	6.38409	0.01593	8.39981
H 10	0.22226	0.00000	0.77613	0.00161	0.77774
H 11	0.45048	0.00000	0.54754	0.00197	0.54952
* Total *	-0.00000	15.99519	41.79166	0.21315	58.00000

Natural Population

Core	15.99519	(99.9700% of 16)
Valence	41.79166	(99.5039% of 42)

*B3PW91/6-311++g(d,p), DMSO solvent.

Table S3 Summary of Natural Population Analysis of CH_3-4NI*

Atom No	Natural Charge	Core	Valence	Rydberg	Total
C 1	0.21604	1.99932	3.75161	0.03303	5.78396
N 2	-0.38431	1.99930	5.37211	0.01290	7.38431
C 3	-0.02358	1.99906	4.00248	0.02203	6.02358
C 4	0.19568	1.99886	3.77311	0.03234	5.80432
N 5	-0.44766	1.99937	5.42651	0.02177	7.44766
H 6	0.24006	0.00000	0.75783	0.00210	0.75994
N 7	0.47545	1.99942	4.46764	0.05748	6.52455
O 8	-0.40268	1.99980	6.38824	0.01464	8.40268
O 9	-0.34488	1.99979	6.32941	0.01568	8.34488
C 10	-0.36527	1.99931	4.35365	0.01232	6.36527
H 11	0.21262	0.00000	0.78593	0.00145	0.78738
H 12	0.21527	0.00000	0.78337	0.00137	0.78473
H 13	0.21263	0.00000	0.78592	0.00145	0.78737
H 14	0.20063	0.00000	0.79751	0.00186	0.79937
Total	0.00000	17.99424	47.77533	0.23043	66.00000

CH_3-4NI Natural Population

Core	17.99424	(99.9680% of 18)
Valence	47.77533	(99.5319% of 48)

*B3PW91/6-311++g(d,p), gas phase.

Table S4 Summary of Natural Population Analysis of CH_3-4NI in DMSO*

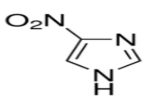
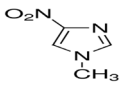
Atom No	Natural Charge	Core	Valence	Rydberg	Total
C 1	0.23522	1.99933	3.73309	0.03236	5.76478
N 2	-0.36218	1.99929	5.35014	0.01275	7.36218
C 3	0.01377	1.99907	3.96630	0.02086	5.98623
C 4	0.18173	1.99890	3.78802	0.03135	5.81827
N 5	-0.49651	1.99939	5.47455	0.02258	7.49651
H 6	0.25257	0.00000	0.74558	0.00185	0.74743
N 7	0.48060	1.99940	4.46414	0.05587	6.51940
O 8	-0.42574	1.99980	6.41111	0.01482	8.42574
O 9	-0.40344	1.99979	6.38769	0.01595	8.40344
C 10	-0.36824	1.99930	4.35650	0.01245	6.36824
H 11	0.22327	0.00000	0.77544	0.00129	0.77673
H 12	0.22604	0.00000	0.77269	0.00126	0.77396
H 13	0.22327	0.00000	0.77544	0.00129	0.77673
H 14	0.21965	0.00000	0.77860	0.00176	0.78035
Total	0.00000	17.99427	47.77928	0.22645	66.00000

CH_3-4NI Natural Population

Core	17.99427	(99.9682% of 18)
Valence	47.77928	(99.5402% of 48)

*B3PW91/6-311++g(d,p), DMSO solvent.

Table S5. Comparison of the geometric parameters of 4-nitroimidazole and 1-methyl-4-nitroimidazole using different DFT functionals.

Parameters	4-NI 			CH_3-4NI 		
	Crystal Struct[a]	Calculated[b]		Crystal Struct[c]	Calculated[b]	
		B3LYP	B3PW91		B3LYP	B3PW91
R_5 /Å	6.756	6.785	6.767	6.661	6.787	6.756
$N_{(1)}$-$C_{(2)}$ /Å	1.357	1.374	1.369	1.323	1.375	1.370
$C_{(2)}$-$N_{(3)}$ /Å	1.317	1.309	1.307	1.354	1.310	1.308
$N_{(3)}$-$C_{(4)}$ /Å	1.367	1.360	1.356	1.267	1.358	1.354
$C_{(4)}$-$C_{(5)}$ /Å	1.360	1.374	1.372	1.409	1.376	1.374
$C_{(5)}$-$N_{(1)}$ /Å	1.355	1.368	1.363	1.308	1.368	1.364
$C_{(4)}$-$N_{(6)}$ /Å	1.428	1.450	1.446	1.433	1.449	1.445
$N_{(6)}$-$O_{(1)}$ /Å	1.236	1.232	1.226	1.248	1.232	1.226
$N_{(6)}$=$O_{(2)}$ /Å	1.234	1.218	1.213	1.125	1.219	1.214
$O_{(1)}$-$N_{(6)}$-$O_{(2)}$ /°	123.3	125.50	125.69	121.20	125.38	125.67
$N_{(6)}$-$C_{(4)}$-$N_{(3)}$ /°	120.7	122.68	122.66	116.95	122.77	122.75
$N_{(1)}$-$C_{(2)}$-$N_{(3)}$ /°	111.9	111.55	111.66	118.15	112.32	112.43

[a][7].

[b] The present calculation using 6-311++G** method in gas phase.

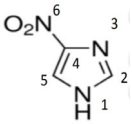
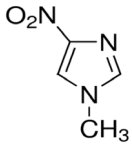
[c][46].

Table S6. ^{1}H, ^{13}C and ^{15}N NMR chemical shift calculations (ppm) of 4-NI and CH_3-4NI*.

Site	Theory						Expt[%]	
	B3LYP		PBE0		M06			
	4-NI	CH_3-4NI	4-NI	CH_3-4NI	4-NI	4-NI(gas)[&]	4-NI	CH_3-4NI
$C_{(2)}$	139.70	142.99	137.03	140.54	130.49	146.01	135.4	137.8
$C_{(4)}$	155.45	156.05	153.58	154.13	151.67	165.23	149.2[a]	147.4
$C_{(5)}$	126.18	129.91	122.85	126.73	115.49	129.13	118.6	121.2
C_{methyl}	-	35.26	-	35.95	-	-	-	35.4
$N_{(1)}$	190.76	204.82	191.62	206.01	174.00	187.55	174.9[c]	173.5[b]
$N_{(3)}$	281.64	280.75	276.46	276.08	288.64	308.83	251.6[c]	244.5[b]
$N_{(6)}$	398.57	398.62	371.74	371.59	379.69	404.70	363.1[c]	-
$H_{(1)}$	9.25	-	9.65	-	8.29	8.22	-	-
$H_{(2)}$	8.10	7.33	7.88	7.64	7.32	7.14	7.8	7.7
$H_{(5)}$	7.56	8.00	8.37	8.27	7.77	7.60	8.2	8.3
$H_{(7)}$	-	3.73	-	4.12	-	-	-	3.8

* Using other DFT functionals in DMSO solvent.
[&] 6-311++G(d,p) basis set.
[%] All experimental measurements are from the present study except where indicated.
[a] McKillop *et al.* [43]measured in CD_3SCCD_3 solvent.
[b] Crystal phase of Ueda *et al.* [9]measured for crystalline sample at room temperature. ^{15}N-NMR are referenced to $^{15}NH_3Cl$ nitrogen (-341.2 ppm) relative to NH_3 at 380.5 ppm.
[c] Chen *et al.* [1]in DMSO/$(CH_3)_2CO$ (3:l) solution for 4-NI.

Table S7. Comparison of the measured ^{13}C and ^{15}N NMR chemical shifts (ppm) for 4-nitroimidazole (4-NI) and 1-methyl-4-nitro-imidazole (CH_3-4NI).

Site	**4-Nitroimidazole** 			**1-Methyl-4-nitroimidazole** 			
	Present* ***(solid-DNP)***	***Present**** ***(soln)***	***Refs*** ***(soln)***	***Present**** ***(solid)***	***Present**** ***(soln)***	***Ref[d] (soln***	***Ref[b,e,g]*** ***(soln)***
$C_{(2)}$	136.4	135.4	136.7[a,g]	137.6	137.5	141.9	136.6[e] (138.6)[g]
$C_{(4)}$	144.7	-	149.2[a,g]	147.5	-	151.8	148.3[e] (147.8)[g]
$C_{(5)}$	119.4	118.6	119.8[a,g]	121.3	122.0	117.9	120.1[e] (123.1)[g]
C_{methyl}	-	-	-	35.6	33.9	-	34.6[e] (42.2)[g]
$N_{(1)}$	181.5 (180.5)[b]	-	174.9[c]	-		182.2	173.5[b]
$N_{(3)}$	237.4 (237.5)[b]	-	251.6[c]	-		256.1	244.5[b]
$N_{(6)}$	363.0	-	363.1[c]	-		360.3	-
$H_{(1)}$		-					
$H_{(2)}$		7.8			7.7		7.76[e]
$H_{(5)}$		8.2			8.3		7.42[e]
$H_{(7)}$		-			3.8		3.83[e]

* Present DNP solid-state NMR measurement at 100 K. Here soln means HSQC in d_6-DMSO solvent so that $C_{(4)}$ resonance is not observed.

[a] McKillop *et al.* [43]measured in CD_3SCCD_3 solvent, likely at room temperature.

[b] Crystalline sample at room temperature measured using ^{15}N cross polarization/magic angle spinning (CP/MAS) NMR spectra of 4-substituted imidazole derivatives. Powdered samples of ^{15}N-enriched glycine (-347.5 ppm from nitromethane) and $^{15}NH_4C1$ (-341.2 ppm) were used as the external standards for the ^{15}N chemical shift [9].

[c] Chen *et al.* [1]in DMSO/$(CH_3)_2CO$ (3:l) solution for 4NI. The ^{15}N-NMR are δ + 380.5 ppm.

[d] Martino *et al.* [53]in DMSO solution for the 1-methyl-4-nitro-5-thioimidazole (MNTI) moiety of nitroprodenafil (NitroproMSild, Structure A in Figure 1).

[e] In $CDCl_3$ solution [45] pointed out that the ^1H-NMR chemical shifts at 3.83 ppm, 4.72 ppm and 7.76 ppm in [54] could be a typing error for 7.42 ppm.

[f] Shchepin RV *et al.*[55] in methanol: aqueous buffer (~1:1). The smaller chemical shift δ in the solution pH<4.6 and the larger in the solution with pH>12.0. The total chemical shift between the pH range is 31.2 ppm.

[g] Lippmma *et al.* [44]in DMSO: the error is ±0.3 ppm for all shifts. The $N_{(1)}$ and $N_{(3)}$ were unable to be measured but grouped as $N_{(ring)}$.

References

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<jrn> [55] R. V. Shchepin, D. A. Barskiy, A. M. Coffey, T. Theis, F. Shi, W. S. Warren, B. M. Goodson, E. Y. Chekmenev, *ACS Sens.* 2016, **1**, 640. doi:10.1021/acssensors.6b00231</jrn>