Electronic Supplementary Material (ESI) for CrystEngComm
This journal is © The Royal Society of Chemistry 2013

Constructing molecular polygons using halogen bonding and bifurcated N-oxides

Christer B. Aakeröy,*[a] Tharanga K. Wijethunga[a] and John Desper[a]

Department of Chemistry, Kansas State University, Manhattan, KS 66506

aakeroy@ksu.edu

Supplementary Information

This journal is © The Royal Society of Chemistry 2013

Table of contents

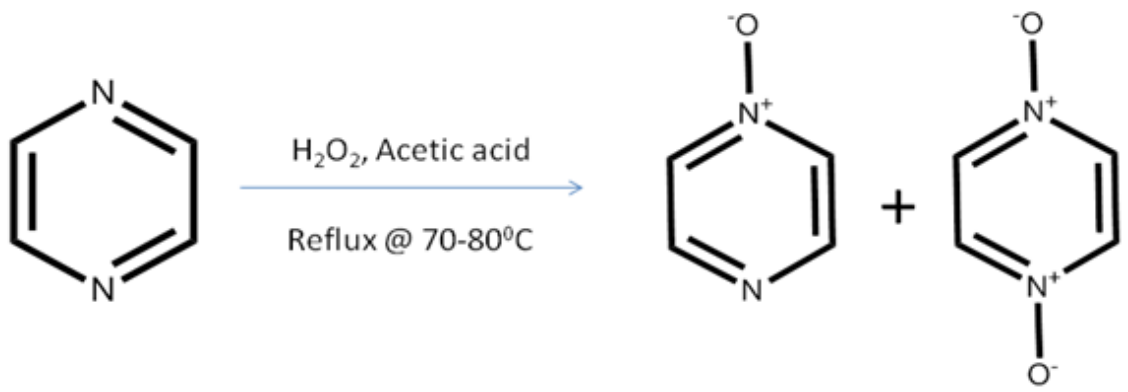
General experimental details

A1 – A3 were prepared using a previously reported method[1]. The method was modified in order to get both mono (**A1** – **A3**) and *bis* (**A7** – **A9**) products at once. **A4 – A6** were purchased from Aldrich chemicals, **A10** was purchased from Acros Organics, **D1, D2, D3** were purchased from Matrix Scientific and **D4** was purchased from TCI America. All these chemicals were used without further purification.

The determinations of melting points were carried out on Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity plus 400 MHz spectrometer in $CDCl_3$ or D6-DMSO. Infrared spectroscopy was carried out on a Nicolet 380 FT-IR.

Synthesis of N-oxides

Synthesis of A1 and A7

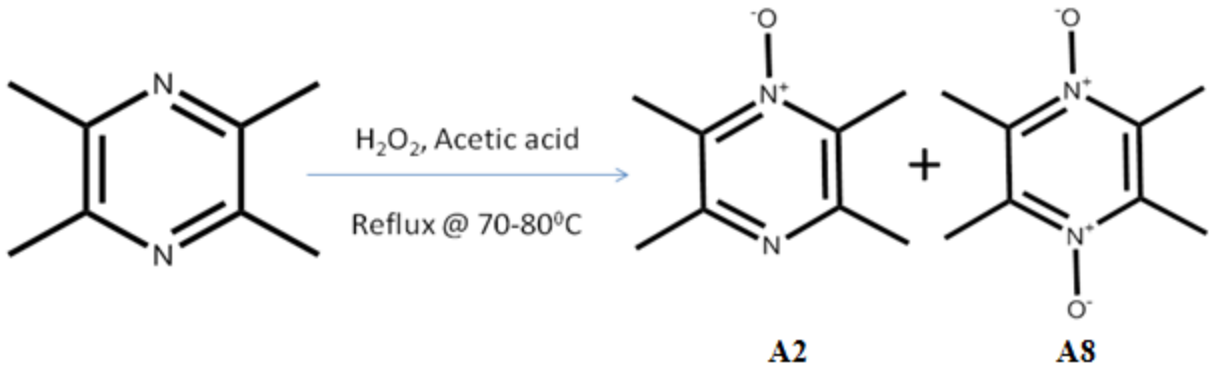


A1 **A7**

A solution of 30% hydrogen peroxide (2.84g, 0.084 mol) in 20 mL of acetic acid was added dropwise using a drop funnel over a period of 2.5 hours to a solution of pyrazine (1.00g, 0.013 mol) in 15 mL of acetic acid at 70-80°C. Refluxing was continued for about 24 hours until the TLC confirmed the presence of two products. Acetic acid was removed on a rotary evaporator, and then 10 mL of water was added followed by evaporation. The residue was dissolved in 50 mL of hot chloroform and dried with a mixture of sodium sulfate and sodium carbonate and the solvent was removed on a rotary evaporator. The residue was chromatographed on silica with

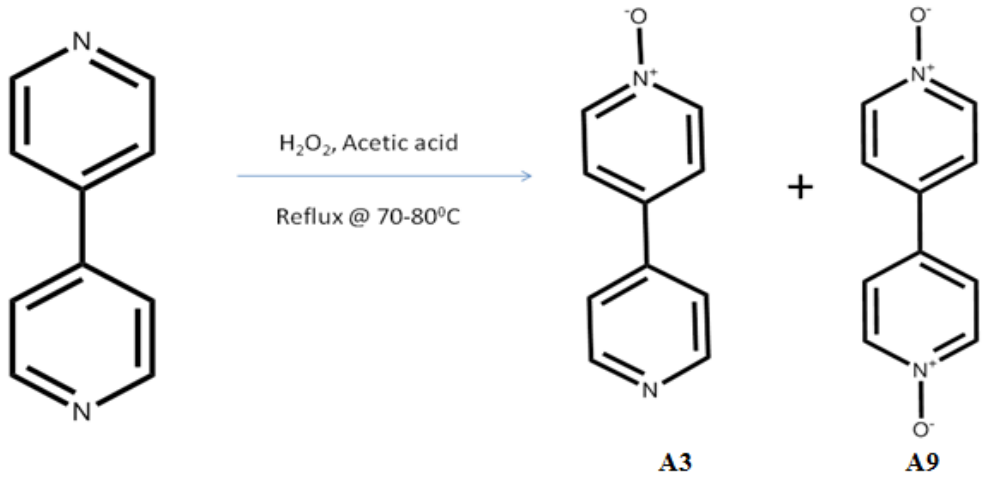
variant ratio mixtures of chloroform-methanol as the eluant. A1 and A7 were isolated as off white solids. **A1** - (0.48g, 77%); m.p.: 110-113^{0}C (Lit. m.p.: 113-115^{0}C)[1]; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 8.09 (d, 2H), 8.45 (d, 2H). A7 - (0.37g, 50%). m.p.: > 300^{0}C; ^{1}H NMR (δH; 400 MHz, DMSO-d_6): 8.27 (s, 4H).

Synthesis of A2 and A8



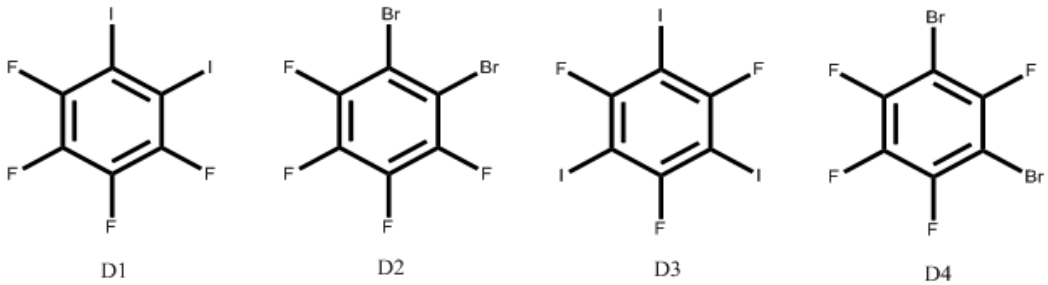
A solution of 30% hydrogen peroxide (2.84g, 0.084 mol) in 20 mL of acetic acid was added dropwise using a drop funnel over a period of 2.5 hours to a solution of tetramethylpyrazine (1.77g, 0.013 mol) in 15 mL of acetic acid at 70-80°C. Refluxing was continued for about 24 hours until the TLC confirmed the presence of two products. Acetic acid was removed using a rotary evaporator, 10 mL of water was added followed by evaporation. The residue was dissolved in 50 mL of hot chloroform and dried with a mixture of sodium sulfate and sodium carbonate and the solvent removed on a rotary evaporator. The residue was chromatographed on silica with variant ratio mixtures of chloroform-methanol as the eluant. **A2** was isolated as a off white solid and **A8** was isolated as pure white solid. **A2** - (0.65g, 66%), m.p.: 98-100^{0}C (Lit. m.p.: 113-115^{0}C)[1]; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 2.45 (d, 6H), 2.50 (d, 6H). **A8** - (0.58g, 53%), m.p.: 220 -222^{0}C; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 2.56 (s, 12H).

Synthesis of A3 and A9



A mixture of 4,4′-Bipyridine (2.00g, 12.82 mmol), 30% hydrogen peroxide (2.66g, 78 mmol) and glacial acetic acid (25 mL) was stirred in a round bottom flask for 24 hours at 70^0C. Reaction was monitored with TLC and after completion, reaction mixture was cooled to room temperature and the solvent was removed via a rotary evaporator and diluted with 20 mL water. The solution was basified with excess sodium carbonate (2g) and extracted with chloroform (3 x 50 mL). The organic layers were combined and then concentrated under reduced pressure using a rotary evaporator. Mixture was further purified via column chromatography with variant mixtures of ethyl acetate-methanol. **A3** and **A9** were isolated as off white solids. **A3** - (0.78g, 70%); m.p.: 170-172^{0}C (Lit. m.p.: 170-171^{0}C)[1]; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 8.74 (d, 2H), 8.73 (d, 2H), 7.55 (d, 2H), 7.53 (d, 2H); **A9** - (0.43g, 34%); m.p.: 97-99^{0}C; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 8.74 (d, 4H), 7.53 (d, 4H).

Halogen bond donors



Synthesis of co-crystals

Grinding experiments

A1-A10 were subjected to grinding experiments with four donors (**D1-D4**). For grinding, 1:1 stoichiometric amounts of acceptors **A1 - A4** and halogen bond donors (**D1-D4**), were mixed together and was grinded using a drop of methanol for several minutes. After the solvent was completely evaporated the IR spectra were recorded. Successful interactions between the acceptor and donor were identified using the specific shifts of the peaks of halogen bond donors, Table S1.

Table S1 : IR analysis of grinding experiments

Mixture	IR bands (cm^{-1})		Shifts Δcm^{-1}	Result
	Halogen bond donors	Grounded Mixture		
A1:D1	1489 1438 813	1486 1430 811	-3 -8 -2	Co-crystal
A1:D2	1498 1459 801	1500 1461 802	+2 +2 +1	No co-crystal
A1:D3	1563 1403 1049	1560 1400 1045	-3 -3 -4	Co-crystal
A1:D4	1484 1446 893	No **D4** present	-	No co-crystal
A2:D1	1489 1438 813	1487 1434 810	-2 -4 -3	Co-crystal
A2:D2	1498 1459 801	1498 1458 801	- -1 -	No co-crystal
A2:D3	1563 1403 1049	1561 1400 1045	-2 -3 -4	Co-crystal
A2:D4	1484 1446 893	1484 1447 893	- +1 -	No co-crystal
A3:D1	1489 1438 813	1480 1428 809	-9 -10 -4	Co-crystal
A3:D2	1498 1459 801	No **D2** present	-	No co-crystal
A3:D3	1563 1403	1561 1394	-2 -9	Co-crystal

	1049	1038	-11	
A3:D4	1484 1446 893	1484 1448 895	- -2 -2	No co-crystal
A4:D1	1489 1438 813	No **D1** present	-	No co-crystal
A4:D2	1498 1459 801	No **D2** present	-	No co-crystal
A4:D3	1563 1403 1049	1560 1397 1043	-3 -6 -6	Co-crystal
A4:D4	1484 1446 893	No **D4** present	-	No co-crystal
A5:D1	1489 1438 813	1488 1436 812	-1 -2 -1	No co-crystal
A5:D2	1498 1459 801	1498 1457 800	- -2 -1	No co-crystal
A5:D3	1563 1403 1049	1560 1397 1036	-3 -6 -13	Co-crystal
A5:D4	1484 1446 893	No **D4** present	-	No co-crystal
A6:D1	1489 1438 813	1481 1429 811	-8 -9 -2	Co-crystal
A6:D2	1498 1459 801	No **D2** present	-	No co-crystal
A6:D3	1563 1403 1049	1560 1399 1044	-3 -4 -5	Co-crystal
A6:D4	1484 1446 893	1482 1445 891	-2 -1 -2	No co-crystal
A7:D1	1489 1438 813	No **D1** present	-	No co-crystal
A7:D2	1498 1459 801	1500 1458 799	+2 -1 +2	No co-crystal
A7:D3	1563 1403 1049	1561 1401 1048	-2 -2 -1	No co-crystal
A7:D4	1484 1446 893	1482 1445 895	-2 -1 +2	No co-crystal
A8:D1	1489 1438 813	1484 1434 811	-5 -4 -2	Co-crystal

A8:D2	1498 1459 801	No **D2** present	-	No co-crystal
A8:D3	1563 1403 1049	1561 1400 1046	-2 -3 -3	Co-crystal
A8:D4	1484 1446 893	No **D4** present	-	No co-crystal
A9:D1	1489 1438 813	1480 1429 803	-9 -9 -10	Co-crystal
A9:D2	1498 1459 801	No **D2** present	-	No co-crystal
A9:D3	1563 1403 1049	1561 1394 1038	-2 -7 -9	Co-crystal
A9:D4	1484 1446 893	1483 1445 893	-1 -1 -	No co-crystal
A10:D1	1489 1438 813	No **D1** present	-	No co-crystal
A10:D2	1498 1459 801	No **D2** present	-	No co-crystal
A10:D3	1563 1403 1049	1560 1399 1048	-3 -4 -1	Co-crystal
A10:D4	1484 1446 893	1484 1445 891	- -1 -2	No co-crystal

Solvent experiments

The solid ground mixtures were dissolved in 2ml of methanol and kept in a slightly open vial for the single crystal formation. Once the crystals are formed they were analyzed using IR spectroscopy and melting point analysis was done. Table S2 includes the melting point results. The IR results were pretty much the same as obtained from grinding experiments.

Table S2: melting point analysis of co-crystals

		$C_6F_4I_2$(1,2) (D1)	$C_6F_3I_3$(1,3,5) (D3)
		49-50	**148.5**
Pyrazine mono-N-oxide (A1)	**110-113**	61-63	122-124
Tetramethyl pyrazine mono-N-oxide (A2)	**98-100**	118-120	155-157
4,4'-bipyridine mono-N-oxide (A3)	**170-172**	183-185	205-208
Pyridine N-oxide (A4)	**65-66**	-	210-212
4-picoline N-oxide (A5)	**182**	-	165-167
3-picoline N-oxide (A6)	**38-40**	120-123	140-143
Pyrazine bis-N-oxide (A7)	**>300**	-	-
Tetramethyl pyrazine bis-N-oxide (A8)	**220-222**	118-120	153-155
4,4'-bipyridine bis-N-oxide (A9)	**97-99**	-	-
2,2'-bipyridine bis-N-oxide (A10)	**296 - 298**	69-74	-

All melting points are reported in ^{0}C.

X-Ray crystallography

Crystallographic data were obtained for the five co-crystals, Table S3-S4.

Table S3: Crystallographic data

	A8:D3	**A4:D3**	**A8:D1**	**A5:D1**	**A6:D1**
Formula moiety	$(C_8H_{12}N_2O_2)$ $(C_6F_3I_3)_2$	(C_5H_5NO) $(C_6F_3I_3)$	$(C_8H_{12}N_2O_2)_2$ $(C_6F_4I_2)_4$	(C_6H_7NO) $(C_6F_4I_2)$	(C_6H_7NO) $(C_6F_4I_2)$
Empirical formula	$C_{20}H_{12}F_6I_6N_2O_2$	$C_{11}H_5F_3I_3NO$	$C_{40}H_{24}F_{16}I_8N_4O_4$	$C_{12}H_7F_4I_2NO$	$C_{12}H_7F_4I_2NO$
Molecular weight	1187.72	604.86	1943.83	510.99	510.99
Color, Habit	colourless prism	colourless plate	colourless cube	colourless prism	colourless prism
Crystal size, mm^3	0.32 x 0.24 x 0.14	0.44 x 0.34 x 0.18	0.26 x 0.24 x 0.22	0.42 x 0.28 x 0.16	0.34 x 0.24 x 0.20
Crystal system	Triclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group, Z	P-1, 1	$P2_1/n$, 4	$P2_1/c$, 4	P-1, 2	$P2_1/c$, 4
a, Å	7.9660(6)	12.4824(12)	14.1359(14)	7.9400(5)	7.8713(9)
b, Å	9.2821(7)	7.3041(7)	15.1116(15)	8.5688(6)	23.203(3)
c, Å	10.1097(8)	15.4872(16)	24.361(3)	11.5503(8)	7.8169(9)
α, °	100.812(3)			89.243(2)	
β, °	106.262(2)	97.536(3)	105.927(3)	83.738(2)	92.019(4)
γ, °	95.408(3)			65.570(2)	
Volume, $Å^3$	696.28(9)	1399.8(2)	5004.2(9)	710.77(8)	1426.8(3)
Density, g/cm^3	2.833	2.870	2.580	2.388	2.379
Temperature, °K	120(2)	120(2)	120(2)	120(2)	120(2)
X-ray wavelength	0.71073	0.71073	0.71073	0.71073	0.71073
μ, mm^{-1}	6.755	6.723	5.064	4.463	4.447
Θ_{min}, °	2.15	2.25	1.60	1.77	1.76
Θ_{max}, °	33.13	32.54	33.14	32.57	32.66
Reflections					
collected	18582	13950	81993	11235	16697
independent	4468	4568	18382	4521	5006
observed	4255	4343	16534	4212	4805
Absorption corr	multi-scan	multi-scan	multi-scan	multi-scan	multi-scan
trans min / max	0.2211 / 0.4515	0.1559 / 0.3775	0.3527 / 0.4021	0.2558 / 0.5354	0.3132 / 0.4700
Threshold expression	>2σ(I)	>2σ(I)	>2σ(I)	>2σ(I)	>2σ(I)
R_1 (observed)	0.0204	0.0249	0.0341	0.0288	0.0221
wR_2 (all)	0.0530	0.0586	0.0816	0.0768	0.0505
S	1.133	1.210	1.025	1.089	1.186
Δρ max / min	1.535 / -0.912	0.854 / -1.792	7.622 / -6.171	2.286 / -0.812	0.704 / -0.679

Table S4: Halogen bonding geometries

Co-crystal	**O···I (Å)**	**N-O···I (^{0})**
A4:D3	2.7413 (0.0019)	105.17 (0.14)
A5:D1	2.8333 (0.0021)	122.02 (0.15)
A8:D1	3.1570 (0.0022)	110.78 (0.16)
	2.9183 (0.0022)	99.57 (0.15)
	2.8538 (0.0023)	111.33 (0.16)
	2.8703 (0.0023)	102.21 (0.16)
A6:D1	2.7729 (0.0017)	108.18 (0.12)
A8:D3	2.8331 (0.0016)	134.23 (0.14)

X-ray data were collected on a Bruker SMART APEX II CCD diffractometer at 120 K using, a fine-focus molybdenum Kα tube. Data were collected using APEX2[(b)] software. Initial cell constants were found by small widely separated "matrix" runs. Scan speed and scan width were chosen based on scattering power and peak rocking curves. Unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT,[(c)] using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Laué symmetry, space group, and unit cell contents were found with XPREP. Data were reduced with SHELXTL.[(d)] The structures were solved in all cases by direct methods without incident. All hydrogen atoms were assigned to idealized positions and were allowed to ride. Heavy atoms were refined with anisotropic thermal parameters. Absorption correction was carried out on all datasets.

(a) SMART v5.060, © 1997 - 1999, Bruker Analytical X-ray Systems, Madison, WI.
(b) APEX2 v2.2.0 © 2005 - 2007, Bruker AXS, Madison, WI.
(c) SAINT v7.46a, © 1997 - 2007, Bruker AXS, Madison, WI.
(d) SHELXTL v6.10, © 2001 , Bruker AXS, Madison, WI.

CSD analysis

CSD analysis was done using the conquest version 1.15 and the CSD version 5.34 (November 2012).

I--O halogen bond analysis

Search criteria was for I---O non bonded interactions with a defined intermolecular bond distance shorter than sum of van der waals radii of two atoms. Structures were filtered with the filters of not disordered, no errors, not polymeric, no ions, no powder structures. A total of 814 hits were found with I--O halogen bonding. Among those structures only 26 are reported as bifurcated bonds with following CSD codes.

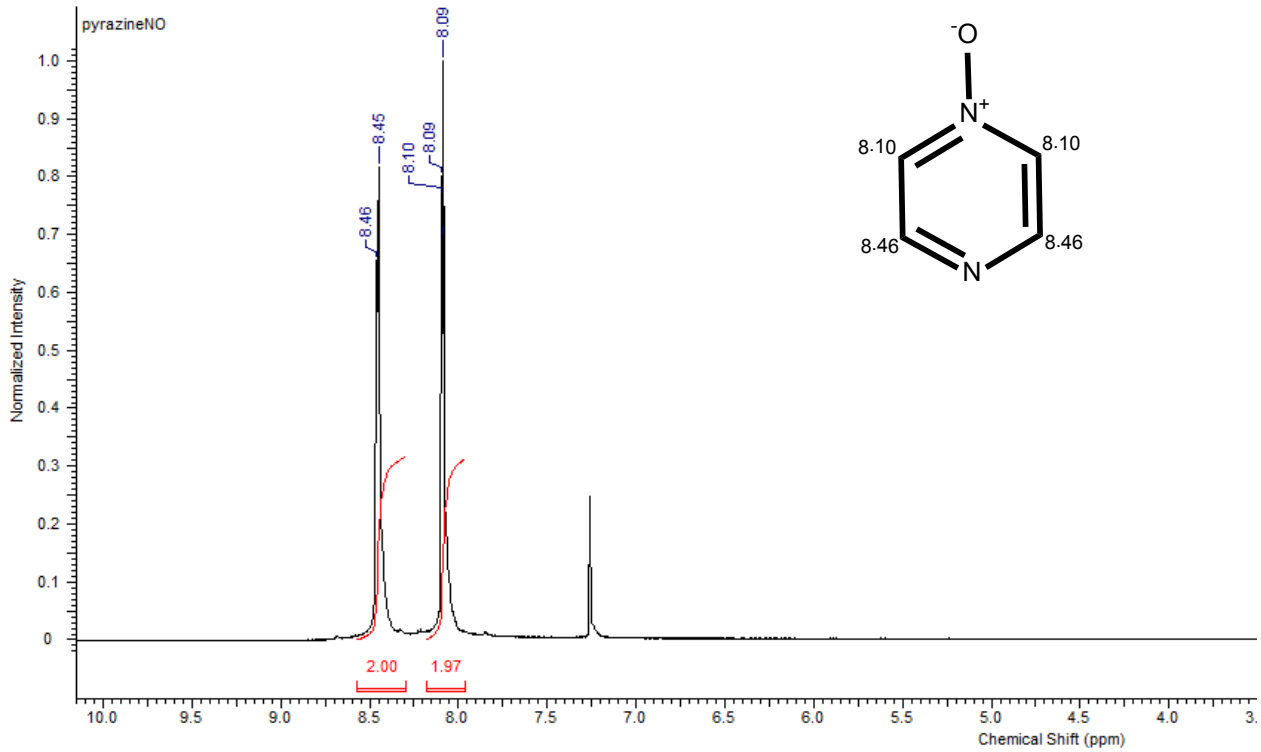
GEHYEZ, AHORIZ, BACDEQ, BEBMEB, CAHZUI, CAMSUF, CIOBEN, DAJTUD, DUWLUD, ETELOF, FAVBEJ, GULYOB, IFORAM, INUZUM, KAFREO, KOVGEH, MASVUZ, MTIXTP, NACSIU, RIMXEQ, RUWRUX, ULOKIP, WIPBUS, XORYIM, ZAVFOR, ZEMKUX.

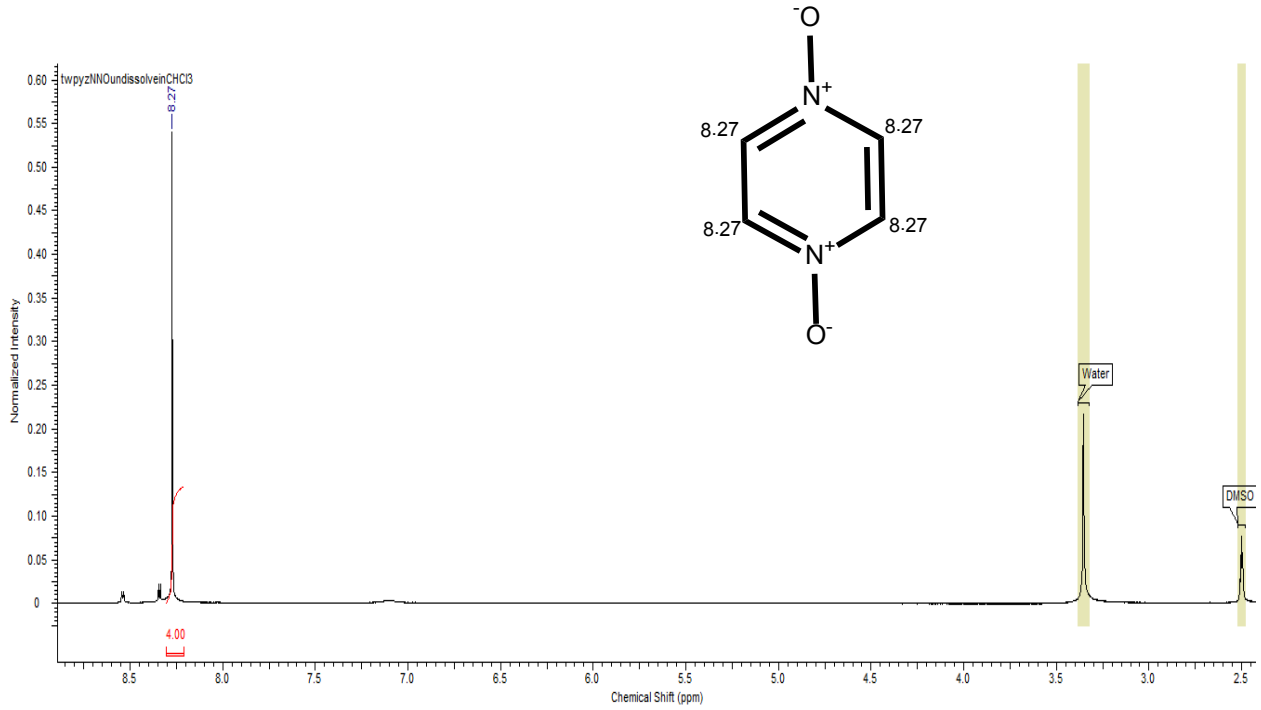
N-oxide halogen bonding

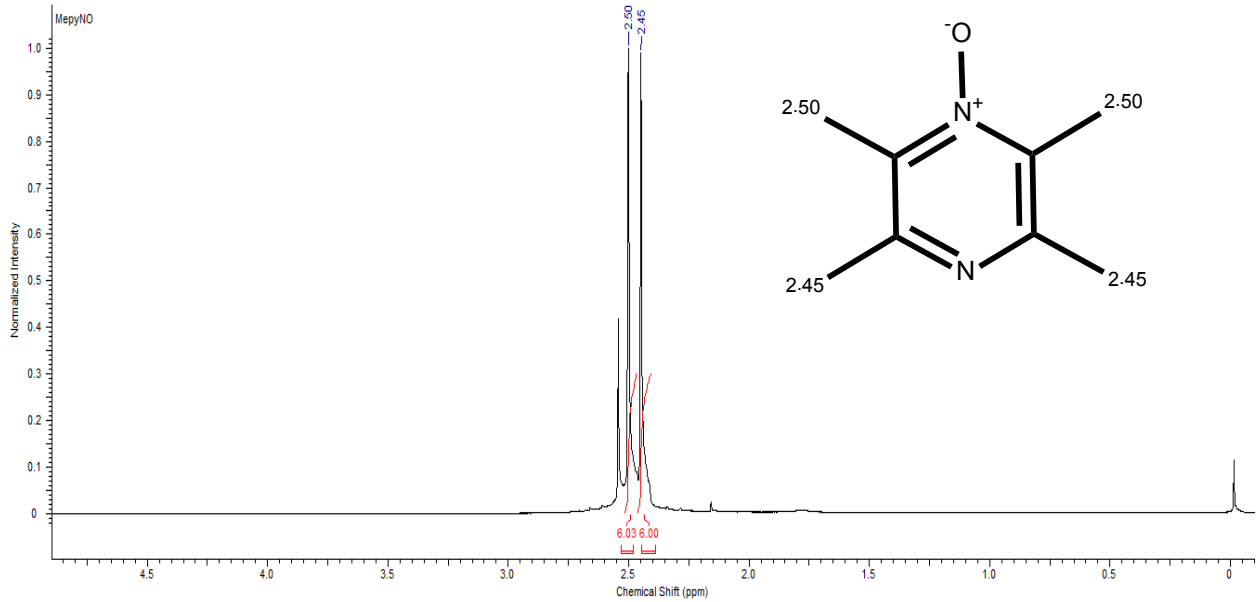
Search criteria was to find N-X intermolecular interactions where X is any halogen and the length of interaction to be less than the sum of van der waals radii of two atoms. All of the above filters were also used. There are only 29 structures in CSD which shows halogen bonding of N-oxides with any of halogen bond donors and none of them are bifurcated. The CSD codes for the 29 structures are as follow.

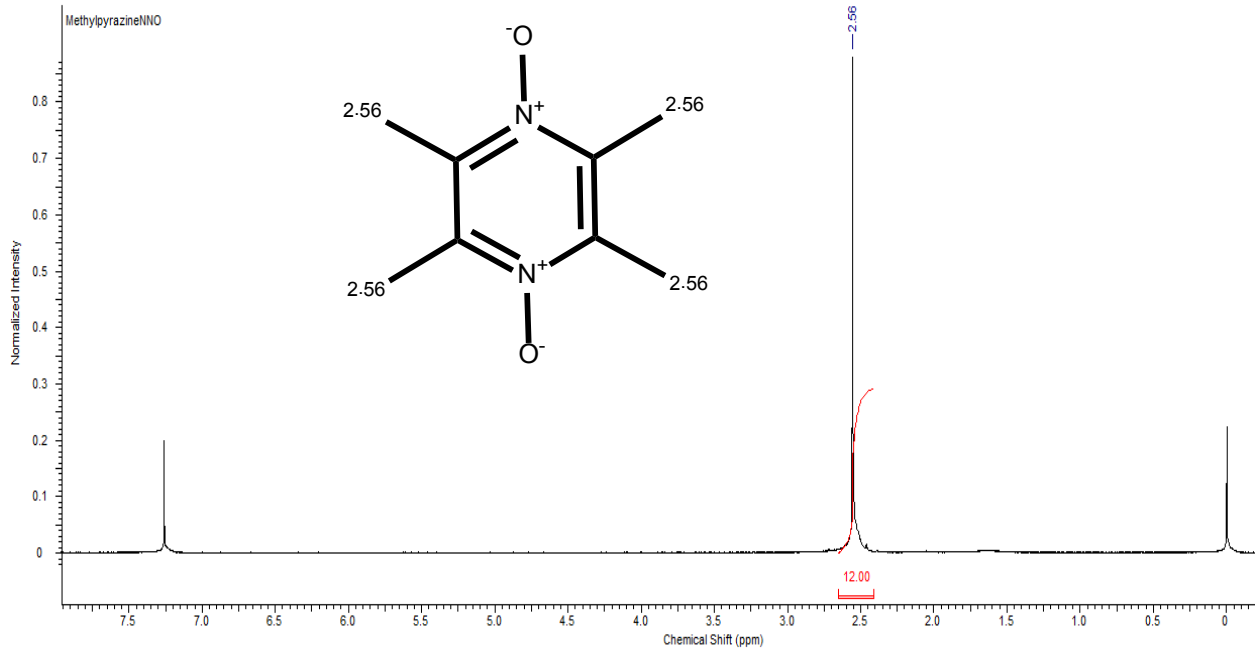
AFECUJ, AFECUJ01, BREMIN, COJJOB, DIXVUB, EHESIT, HERBAH, HUFTEH, IBZFRO, IHUNAB, KOYPOD01, MBODZO10, MEXRAI, OCOMUO, OCOMUO01, OCOMUO02, OCOMUO03, OCOMUO04, OCOMUO05, OQOYOJ, OQUJIU, SAHDOV, SILNIL, TAKBAJ, XIHCOG, XIMVAR, XIVWOO, YISZUV, YOFXEX

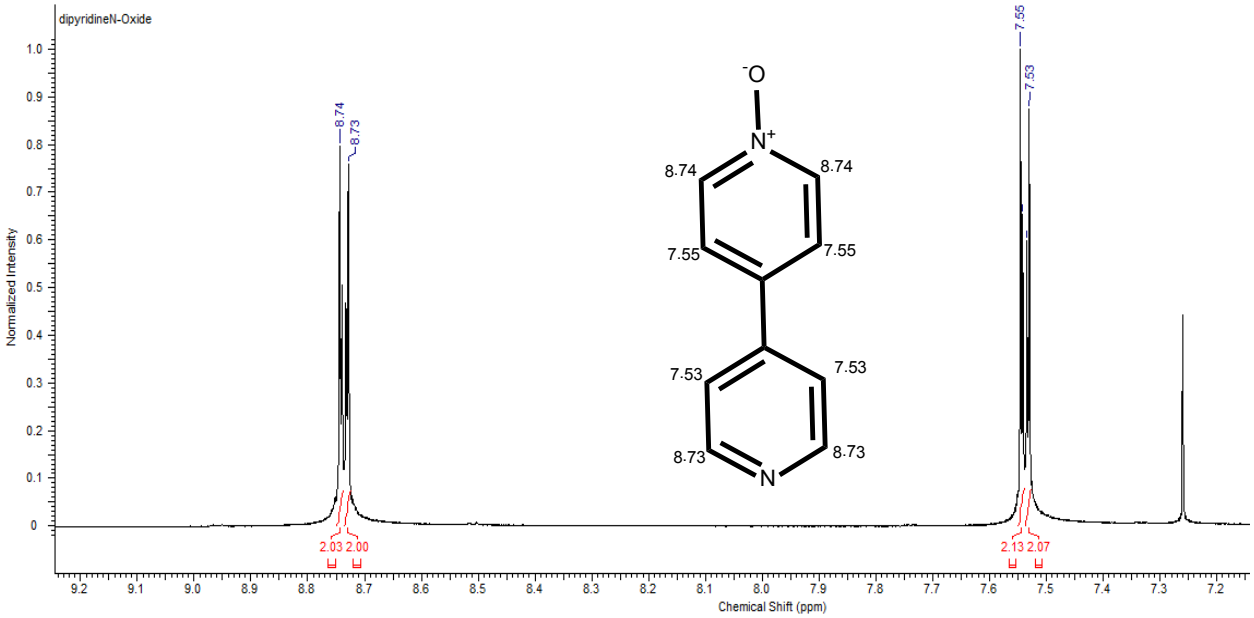
NMR data

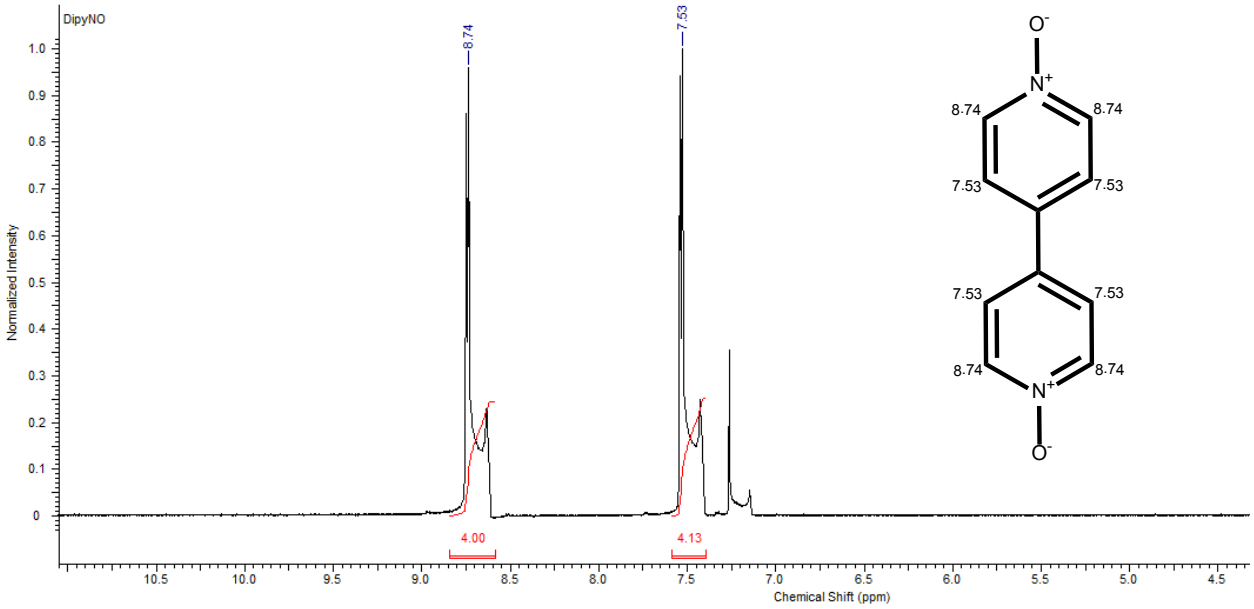

pyrazineNO
8.09
8.45
8.10
8.09
8.46
2.00
1.97
Normalized Intensity
Chemical Shift (ppm)
-O
N+
8.10
8.10
8.46
8.46
N


twpyzNNOundissolveinCHCl3
8.27
4.00
Water
DMSO
Normalized Intensity
Chemical Shift (ppm)
-O
N+
8.27
8.27
8.27
8.27
N+
O-


MepyNO
2.50
2.45
6.03
6.00
Normalized Intensity
Chemical Shift (ppm)
-O
N+
N
2.50
2.50
2.45
2.45


MethylpyrazineNNO
2.56
12.00
Normalized Intensity
Chemical Shift (ppm)
-O
N+
N+
O-
2.56
2.56
2.56
2.56





[1] S. Forbes, *Hydrogen bonded driven supramolecular chemistry for modulating physical properties of pharmaceutical compounds*, 2010, Ph.D. thesis, Kansas State University