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Significant determinants of isotope composition during HI/P_{red} synthesis of methamphetamine.

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Table S-1. Eight-run Plackett-Burman experimental design set-up to study up to seven reaction variables. The high and low levels of the variables are shown as +1 and -1.

	Reaction Variable													
	A		B		C		D		E			F	G	
	Precursor		Scale (g)		Temp (°C)		Time (h)		H-donor					
	+1	-1	+1	-1	+1	-1	+1	-1	+1		-1	+1	-1	
	PE2	PE1	5	0.5	115	165	4	0.5	H2O-1, HIA-1, HYPO-1		H2O-2, HIA-2, HYPO-2	Dummy variables		
PB run	A		B		C		D		E			F	G	
1	-1		-1		-1		+1		+1			+1	-1	
2	+1		-1		-1		-1		-1			+1	+1	
3	-1		+1		-1		-1		+1			-1	+1	
4	+1		+1		-1		+1		-1			-1	-1	
5	-1		-1		+1		+1		-1			-1	+1	
6	+1		-1		+1		-1		+1			-1	-1	
7	-1		+1		+1		-1		-1			+1	-1	
8	+1		+1		+1		+1		+1			+1	+1	

Table S-2. Yield, percent carbon (C±0.6 %) and nitrogen (N±0.2 %), and IRMS (δ^2H_{VSMOW} ±4‰, $\delta^{13}C_{VPDB}$ ±0.2‰, $\delta^{15}N_{AIR}$ ±0.2‰) results for samples produced by methods A, B and C. Calc. for $C_{10}H_{15}N.HCl$: C 64.6, N, 7.5 %.

Sample	PB Run	Yield, g (%)	C	N	δ^2H	$\delta^{13}C$	$\delta^{15}N$
PA13	1	0.1705 (37)	66.1	7.4	72	-23.4	6.4
PA16	2	0.1904 (41)	60.8	6.9	-32	-28.5	9.0
PA7	3	0.4052 (9)	66.1	7.7	95	-23.6	1.9
PA6	4	0.9822 (21)	63.5	7.4	-55	-28.4	17.7
PA9	5	0.3163 (68)	64.0	7.4	132	-23.6	6.6
PA2	6	0.2729 (59)	62.3	7.2	-125	-29.0	5.9
PA14	7	0.6313 (14)	57.5	6.6	107	-23.4	2.7
PA5	8	1.4438 (31)	60.5	7.0	-127	-29.5	6.2
PA4	1 (duplicate)	0.1756 (38)	63.9	7.4	85	-23.3	7.0
PA8	2 (duplicate)	0.2316 (50)	64.2	7.3	-28	-28.5	6.5
PA15	3 (duplicate)	0.4701 (10)	58.4	6.7	94	-23.5	0.2
PA11	4 (duplicate)	2.1557 (46)	63.7	7.3	-73	-28.4	6.0
PA3	5 (duplicate)	0.2159 (47)	64.3	7.5	126	-23.3	6.8
PA12	6 (duplicate)	0.1919 (41)	63.4	7.3	-138	-29.4	6.8
PA10	7 (duplicate)	1.86 (41)	55.5	6.4	130	-23.2	3.0
PA1	8 (duplicate)	1.8595 (40)	63.0	7.3	-122	-29.2	8.2
PB7	1	0.2908 (63)	64.1	7.4	78	-23.7	5.0
PB6	2	0.1753 (38)	64.6	7.5	-120	-28.7	7.1
PB11	3	0.6678 (15)	58.3	6.8	111	-23.1	3.9
PB9	4	2.0342 (44)	65.6	7.8	-108	-28.8	9.8
PB13	5	0.2949 (64)	65.9	7.4	70	-23.4	5.8
PB8	6	0.1211 (26)	58.7	7.1	-96	-27.2	6.7
PB2	7	1.4781 (32)	59.5	6.9	103	-24.2	5.0
PB10	8	0.7207 (16)	59.6	7.0	-105	-28.5	5.2
PB4	1 (duplicate)	0.2745 (59)	64.5	7.4	81	-23.7	5.7

PB1	2 (duplicate)	0.2645 (57)	64.1	7.3	-117	-28.9	6.6
PB14	3 (duplicate)	0.4204 (9)	58.0	6.6	110	-23.3	3.5
PB15	4 (duplicate)	1.5986 (35)	65.3	7.4	-101	-28.4	11.7
PB12	5 (duplicate)	0.2572 (55)	66.3	7.3	71	-23.5	5.7
PB5	6 (duplicate)	0.1748 (38)	61.3	7.0	-121	-29.2	5.7
PB16	7 (duplicate)	0.1451 (3)	54.6	6.2	168	-21.5	6.2
PB3	8 (duplicate)	1.1519 (25)	60.2	7.1	-103	-29.1	6.4
PC1	1	0.3183 (69)	60.5	6.8	69	-23.5	6.8
PC9	2	0.3434 (74)	66.7	7.3	-123	-28.6	7.7
PC15	3	2.1358 (47)	65.4	7.4	72	-24.2	7.9
PC14	4	3.0017 (65)	66.4	7.3	-120	-28.6	7.7
PC13	5	0.3219 (70)	65.6	7.4	83	-23.5	6.5
PC7	6	0.2882 (62)	65.5	7.4	-128	-29.0	8.4
PC16	7	2.0389 (45)	63.8	7.2	80	-24.4	5.7
PC5	8	2.8781 (62)	65.9	7.4	-134	-28.9	7.6
PC11	1 (duplicate)	0.3279 (71)	61.8	7.0	81	-23.6	5.9
PC2	2 (duplicate)	0.3711 (80)	64.9	7.3	-113	-28.6	7.2
PC10	3 (duplicate)	2.5381 (56)	69.0	7.4	73	-24.1	7.3
PC4	4 (duplicate)	2.5774 (56)	65.8	7.4	-112	-28.7	9.1
PC12	5 (duplicate)	0.2825 (62)	66.1	7.4	92	-23.4	7.3
PC6	6 (duplicate)	0.3143 (68)	66.0	7.4	-129	-28.7	8.2
PC3	7 (duplicate)	0.1187 (3)	57.2	6.5	106	-24.2	1.4
PC8	8 (duplicate)	2.8278 (61)	66.4	7.4	-133	-28.8	8.8

Table S-3. Plackett-Burman analysis results for method A.

Isotope	Rank	*z* value (4.s.f)	Initial Run			Duplicate Run		
			Variable	Effect	t-test	Variable	Effect	t-test
^{2}H	1	-1.150	A	-186	1.33.10-4	A	-199	1.88.10-4
	2	-0.6745	E	-59	9.93.10-3	E	-59	0.017
	3	-0.3186	C	-23	0.147	C	-20	0.24
	4	-1.391.10-16	F	-7	0.629	D	-10	0.52
	5	0.3186	B	-7	0.630	B	-4	0.81
	6	0.6745	D	-6	0.684	F	14	0.40
	7	1.150	G	17	0.259	G	16	0.35
^{13}C	1	-1.150	A	-5.4	1.6.10-5	A	-5.5	3.10-7
	2	-0.6745	E	-0.4	0.98	E	-0.5	3.9.10-3
	3	-0.3186	C	-0.4	0.98	C	-0.4	0.012
	4	-1.391.10-16	G	-0.3	0.98	G	-0.1	0.50
	5	0.3186	B	-0.1	0.99	B	0.1	0.54
	6	0.6745	D	-0.1	0.99	D	0.1	0.31
	7	1.150	F	-0.0	0.99	F	0.1	0.29
^{15}N	1	-1.150	E	-3.9	0.78	B	-2.4	0.049
	2	-0.6745	C	-3.4	0.81	G	-0.3	0.78
	3	-0.3186	G	-2.2	0.87	E	-0.1	0.95
	4	-1.391.10-16	F	-1.9	0.89	F	1.2	0.24
	5	0.3186	B	0.2	0.99	C	1.2	0.23
	6	0.6745	D	4.3	0.75	A	2.6	0.04
	7	1.150	A	5.3	0.064	D	2.9	0.03

Table S-4. Plackett-Burman analysis results for method B

Isotope	Rank	*z* value (4.s.f)	Initial Run			Duplicate Run		
			Variable	Effect	t-test	Variable	Effect	t-test
^{2}H	1	-1.150	A	-197	3.10-6	A	-218	2.10-4
	2	-0.6745	D	-16	0.04	D	-23	0.2
	3	-0.3186	F	-5	0.4	G	-16	0.4
	4	-1.391.10-16	G	-5	0.4	E	-13	0.5
	5	0.3186	C	3	0.6	C	10	0.6
	6	0.6745	E	11	0.1	F	17	0.4
	7	1.150	B	17	3.10-2	B	40	0.07
^{13}C	1	-1.150	A	-4.7	7E-4	A	-5.9	1.10-4
	2	-0.6745	F	-0.7	0.2	E	-0.8	0.1
	3	-0.3186	B	-0.4	0.5	G	-0.5	0.3
	4	-1.391.10-16	D	-0.3	0.6	D	-0.4	0.3
	5	0.3186	G	0.1	0.9	C	0.3	0.6
	6	0.6745	C	0.0	0.7	F	0.3	0.5
	7	1.150	E	0.6	0.3	B	0.8	0.1
^{15}N	1	-1.150	E	-1.7	0.2	E	-2.3	0.2
	2	-0.6745	G	-1.1	0.3	G	-1.8	0.2
	3	-0.3186	F	-0.9	0.4	C	-0.9	0.5
	4	-1.391.10-16	C	-0.8	0.5	F	-0.4	0.8
	5	0.3186	B	-0.2	0.9	B	1.1	0.5
	6	0.6745	D	0.7	0.5	D	1.9	0.2
	7	1.150	A	2.3	0.09	A	2.3	0.1

Table S-5. Plackett-Burman analysis results for method C

Isotope	Rank	*z* value (4.s.f)	Initial Run			Duplicate Run		
			Variable	Effect	t-test	Variable	Effect	t-test
^{2}H	1	-1.150	A	-203	2.10-7	A	-209	4.10-6
	2	-0.6745	E	-10	0.02	E	-20	0.03
	3	-0.3186	F	-4	0.2	G	-7	0.3
	4	-1.391.10-16	B	-1	0.8	D	-2	0.7
	5	0.3186	D	-1	0.8	B	1	0.9
	6	0.6745	G	-1	0.8	C	2	0.8
	7	1.150	C	1	0.8	F	5	0.5
^{13}C	1	-1.150	A	-4.9	1.10-7	A	-4.9	2.10-7
	2	-0.6745	B	-0.4	2.10-3	B	-0.4	6.10-3
	3	-0.3186	C	-0.2	0.01	E	-0.1	0.3
	4	-1.391.10-16	E	-0.1	0.08	F	-0.1	0.3
	5	0.3186	F	-0.1	0.4	C	-0.1	0.4
	6	0.6745	G	0.1	0.3	G	0.1	0.4
	7	1.150	D	0.4	1.10-3	D	0.3	0.02
^{15}N	1	-1.150	F	-0.6	0.3	F	-2.1	0.3
	2	-0.6745	C	-0.4	0.4	C	-0.9	0.6
	3	-0.3186	D	-0.3	0.6	B	-0.5	0.8
	4	-1.391.10-16	B	-0.1	0.8	.10	1.3	0.5
	5	0.3186	G	0.3	0.6	G	1.5	0.5
	6	0.6745	.10	0.8	0.2	D	1.7	0.4
	7	1.150	A	1.1	0.1	A	2.9	0.2

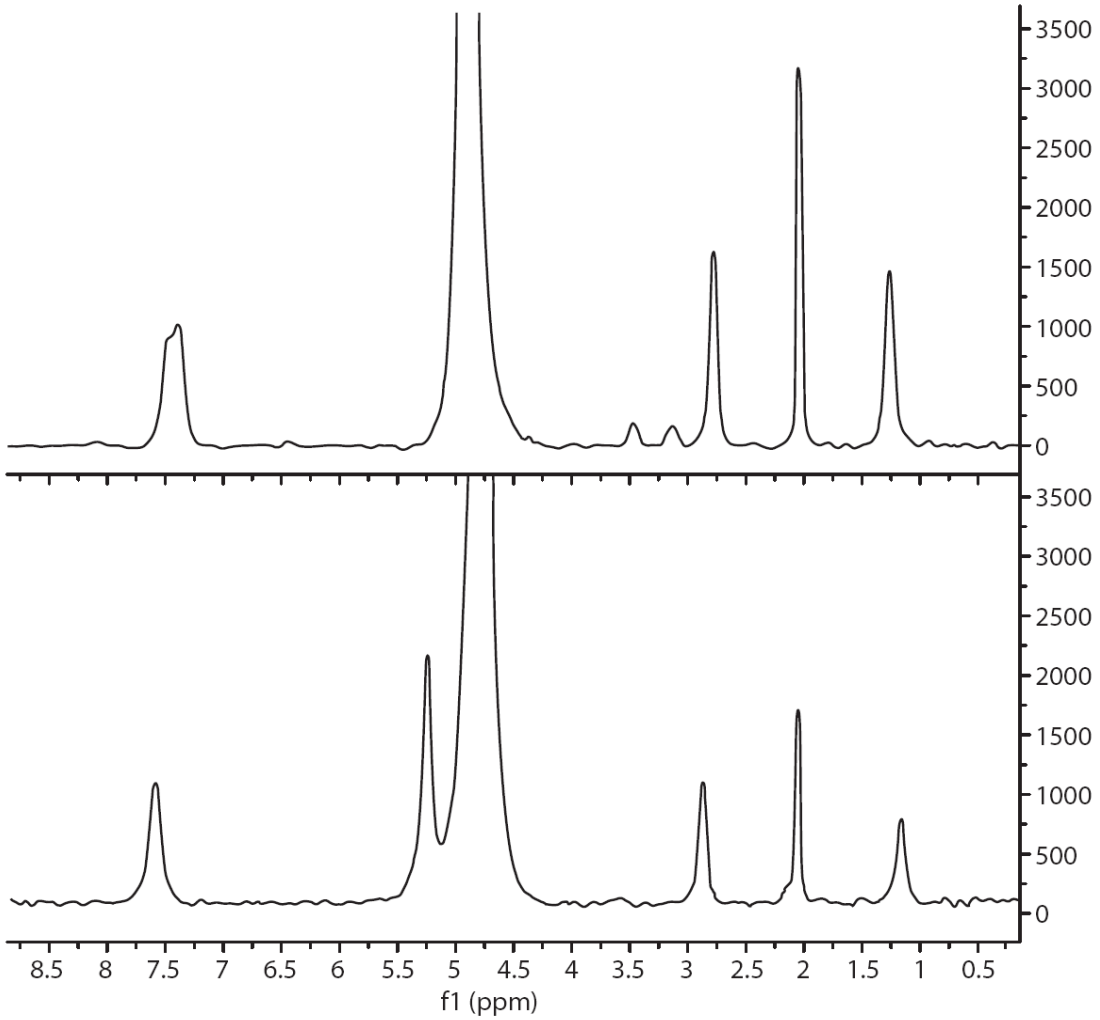

Figure S-1. Top; a representative ^{2}H NMR spectrum of methamphetamine/HCl in water. The peaks in the spectrum from low field to high field can be assigned as; phenyl, water, methine, benzyl, *N*-methyl, acetonitrile, methyl.
Bottom; a representative ^{2}H NMR spectrum of ephedrine/HCl in water. The peaks in the spectrum from low field to high field can be assigned as; phenyl, benzyl, water, *N*-methyl, acetonitrile, methyl. The methine signal is not observed in this spectrum but would be around 3.56 ppm.

Initial Run Duplicate run

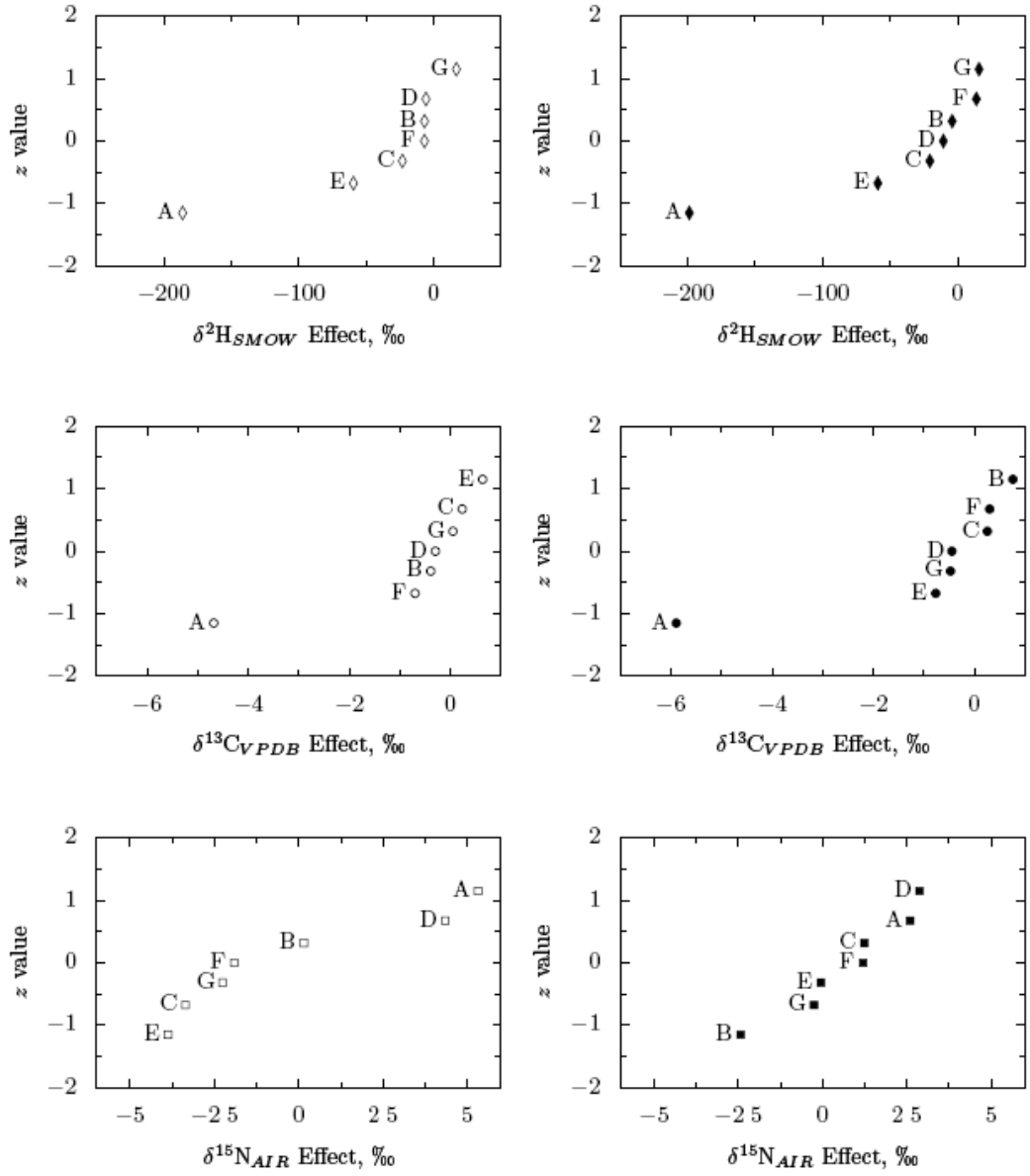

Figure S-2. Plackett-Burman for method A, $\delta^{2}H$, $\delta^{13}C$ and $\delta^{15}N$ Rankit results.

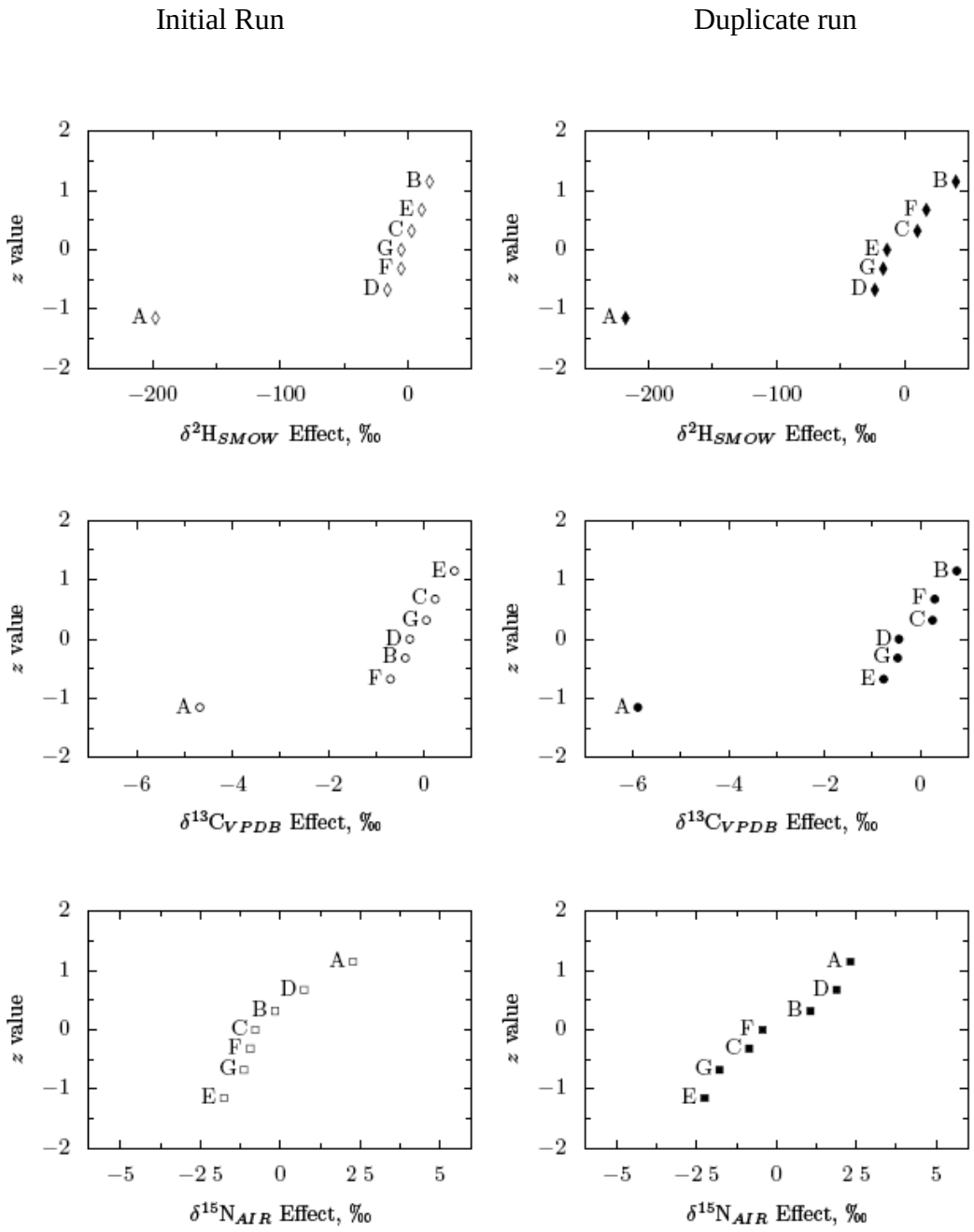

Figure S-3. Plackett-Burman for method B, $\delta^{2}H$, $\delta^{13}C$ and $\delta^{15}N$ Rankit results.

Initial Run Duplicate run

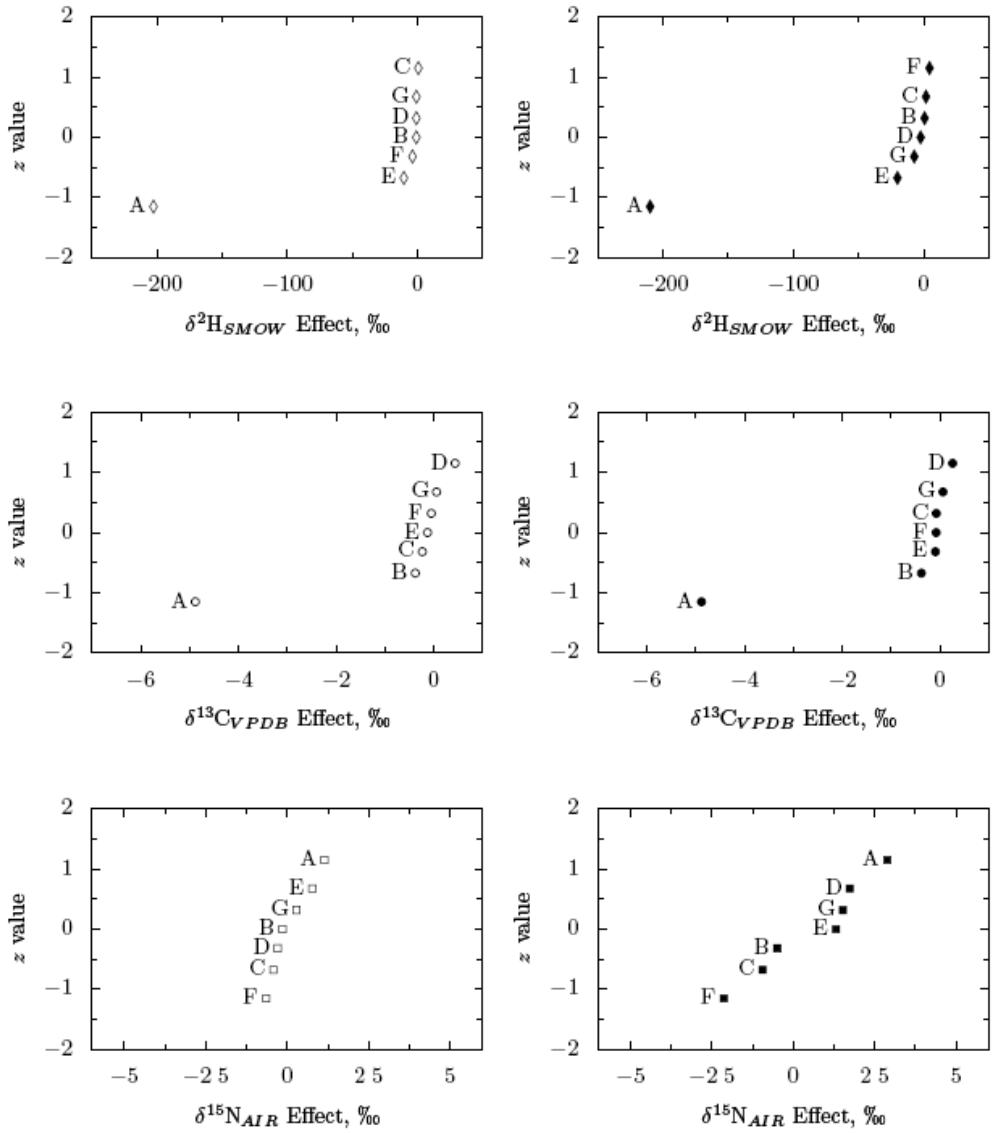

Figure S-4. Plackett-Burman for method C, $\delta^{2}H$, $\delta^{13}C$ and $\delta^{15}N$ Rankit results.

Table S-6. Individual ^{2}H NMR results for ESR samples.

Sample	$\delta^{2}H_{VSMOW}$ ‰	$(D/H)_I$ ppm				
		phenyl	benzyl	methine	*N*-methyl	methyl
E1	122	124.3	822.8	16.8	131.2	116.3
E1[A]		122.4	808.6	9.4	129.6	107.6
E2	133	122.0	787.9	0[B]	124.6	109.8
M1	92	130.6	302.1	21.8	198.9	102.2
M2	103	121.9	294.7	38.6	195.3	108.3
M2[A]		138.8	314.6	78.7	218.8	123.3
M3	91	121.4	318.5	0[B]	195.3	108.5
M4	75	118.6	320.2	0[B]	195.1	108.7
M5	86	136.3	325.0	62.6	207.6	109.3

A– duplicate NMR anaysis. *B* – signal not detected.