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Preparation of *N*-phenyl-*p*-phenylenediamine by coupling of aniline and nitrobenzene in KOH–poly(ethylene glycol) medium

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Contents

General Methods

Aniline and nitrobenzene were purified by distillation. Potassium hydroxide (purum)[*] was obtained from Albemarle corporation, lithium hydroxide and sodium hydroxide were obtained from Merck KGaA, 10% palladium on charcoal (Pd/C), benzophenone, poly(ethylene glycol) (PEG 600, 1000, 1280, 1500, 2000, 3400, 4000, 6000 and 8000 were obtained from Sigma-Aldrich company.

^{1}H and ^{13}C spectra were recorded with Avance-400 spectrometers for solutions in deuterated chloroform. Chemical shifts for ^{1}H and ^{13}C were measured relative to TMS.

Analytical and semi-preparative reversed-phase liquid chromatography was performed with a Waters Delta 600 HPLC system including 996 Photodiode Array Detector, Symmetry C18 column (Waters, 60 Å, 5 μm, 4.6 × 250 mm) using methanol-water mixture (3:2) as a mobile phase. For quantitative purpose, yields of the products (4-nitrosophenyl-*p*-phenylenediamine, 4-nitrophenyl-*p*-phenylenediamine) and by-product (azobenzene) were calculated by the Waters Millenium program as average of three independent runs with internal standard (benzophenone). Calculations were performed based on absorption peaks as shown in Table S1, prepared calibration solutions as shown in Table S2 and calibration data as shown in Table S3, S4 and S5. The relative detectable quantities of the *p*-nitrosodiphenylamine **(1)** and *p*-nitrodiphenylamine **(2)** are in the range from 0.2 to 100%; the relative error for confidence factor 0.95 is ± 2%.

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[*] According to the Certificate of Analysis the content of KOH is 90.1 wt%, see S16 at the end of SM

Calibration data for HPLC analyses

Table S1 Retention times and absorption peaks for products and standard used.*

Compounds to be analyzed	**Retention times t., min**	**Absorption peaks λ, nm**
p-Nitrosodiphenylamine **(1)**	9.9±0.1	**262.0**; 437.4
p-Nitrodiphenylamine **(2)**	18.8±0.3	198.7; **256.2**; 404.8
Benzophenone (internal standard)	15.0±0.2	**248.1**

** Bold digits indicate integrated absorption peaks, the eluent flow rate is 1,4 ml/min*

Table S2 Calibration solutions with internal standard.

Solutions	**1**	**2**	**3**	**4**	**5**	**6**
Internal standard (benzophenone), mg	520.6	501.1	481.4	535.7	525.2	532.3
Concentration of the internal standard, mg/ml	20.82	20.04	19.26	21.43	21.01	21.29
p-Nitrodiphenylamine **(2)**, mg	476.7	770.0	990.3	225.0	122.9	55.0
Concentration of *p*-nitrodiphenylamine **(2)**, mg/ml	19.04	30.80	39.61	9.000	4.916	2.20
p-Nitrodiphenylamine **(2)** / internal standard ratio m/m_{st}	0.9157	1.537	2.057	0.4760	0.2340	0.1033
p-Nitrosodiphenylamine **(1)**, mg	730.8	277.6	543.1	124.1	51.8	81.4
Concentration of *p*-nitrosodiphenylamine **(1)**, mg/ml	29.23	11.10	21.72	4.964	2.07	3.26
p-Nitrosodiphenylamine **(1)**/ internal standard ratio m/m_{st}	1.404	0.5540	1.129	0.2317	0.09863	0.1529

Table S3 Calibration data series 1.

Solutions		*p*-Nitrodiphenylamine **(2)**	*p*-Nitrosodiphenylamine **(1)**	Internal standard (benzophenone)
1	$m/m_{st.}$	0.9157	1.404	—
	Peak integral I	2.874	3.813	6.351
	Intergral ratio $I/I_{st.}$	0.4525	0.6004	—
2	m/m_{st}	1.537	0.5540	—
	Peak integral I	4.713	1.480	6.206
	Intergral ratio $I/I_{st.}$	0.7594	0.2385	—
3	m/m_{st}	2.057	1.129	—
	Peak integral I	6.090	2.925	6.074
	Intergral ratio $I/I_{st.}$	1.003	0.4816	—
4	m/m_{st}	0.4760	0.2317	—
	Peak integral I	1.563	0.6698	6.707
	Intergral ratio $I/I_{st.}$	0.2330	0.09999	—
5	m/m_{st}	0.2340	0.09863	—
	Peak integral I	0.7513	0.2806	6.613
	Intergral ratio $I/I_{st.}$	0.1136	0.04243	—
6	m/m_{st}	0.1033	0.1529	—
	Peak integral I	0.3288	0.4408	6.788
	Intergral ratio $I/I_{st.}$	0.04844	0.06494	—

Table S4 Calibration data series 2.

Solutions		*p*-Nitrodiphenylamine **(2)**	*p*-Nitrosodiphenylamine **(1)**	Internal standard (benzophenone)
1	$m/m_{st.}$	0.9157	1.404	—
	Peak integral I	2.842	3.784	6.383
	Intergral ratio $I/I_{st.}$	0.4452	0.5928	—
2	m/m_{st}	1.537	0.5540	—
	Peak integral I	4.621	1.457	6.173
	Intergral ratio $I/I_{st.}$	0.7486	0.2360	—
3	m/m_{st}	2.057	1.129	—
	Peak integral I	6.196	2.905	6.083
	Intergral ratio $I/I_{st.}$	1.019	0.4776	—
4	m/m_{st}	0.4760	0.2317	—
	Peak integral I	1.626	0.6735	6.928
	Intergral ratio $I/I_{st.}$	0.2347	0.09721	—
5	m/m_{st}	0.2340	0.09863	—
	Peak integral I	0.6143	0.2223	5.356
	Intergral ratio $I/I_{st.}$	0.1147	0.4150	—
6	m/m_{st}	0.1033	0.1529	—
	Peak integral I	0.2658	0.3487	5.421
	Intergral ratio $I/I_{st.}$	0.4903	0.06432	—

Table S5 Calibration data series 3.

Solutions		*p*-Nitrodiphenylamine **(2)**	*p*-Nitrosodiphenylamine **(1)**	Internal standard (benzophenone)
1	$m/m_{st.}$	0.9157	1.404	—
	Peak integral I	2.516	3.333	5.625
	Intergral ratio $I/I_{st.}$	0.4473	0.5925	—
2	m/m_{st}	1.537	0.5540	—
	Peak integral I	4.036	1.261	5.398
	Intergral ratio $I/I_{st.}$	0.7477	0.2336	—
3	m/m_{st}	2.057	1.129	—
	Peak integral I	4.989	2.368	4.967
	Intergral ratio $I/I_{st.}$	1.004	0.4767	—
4	m/m_{st}	0.4760	0.2317	—
	Peak integral I	1.384	0.5932	6.707
	Intergral ratio $I/I_{st.}$	0.2293	0.09828	—
5	m/m_{st}	0.2340	0.09863	—
	Peak integral I	0.7120	0.2666	6.613
	Intergral ratio $I/I_{st.}$	0.1123	0.04204	—
6	m/m_{st}	0.1033	0.1529	—
	Peak integral I	0.2681	0.3533	5.419
	Intergral ratio $I/I_{st.}$	0.04947	0.06520	—

Experimental procedures

Step1. General procedure for reaction of nitrobenzene and aniline

The 250 ml reactor with a mechanical stirrer was charged with PEG 4000 (35 g) and potassium hydroxide (5.88 g, 95 mmol). For dissolving of KOH small amount of methanol (3 ml) was added and the mixture was heated to 120 °C under vigorous stirring for 20 min. The clean homogeneous solution obtained was cooled to 60 °C and aniline (60 ml, 0.65 mol) was added by one portion. Then the reactor was connected to vacuum line and under the pressure 60 mBar dry air was bubbled trough the reaction mixture at constant flow rate 375 ml/min. Using the syringe pump, nitrobenzene (8.85 g, 72 mmol) was introduced to the reactor with rate 0.1 ml/min keeping the temperature at 60 °C. After additional 1 h, the excess of aniline was removed by distillation under the pressure 0.1 mBar and the residue was neutralized with the solution of HCl (10 N, 10.5 ml) giving rise to a solution of *p*-nitrosodiphenylamine **(1)*** (10.83 g, 75.9%) and *p*-nitrodiphenylamine **(2)*** (3.85 g, 20.3%) in PEG 4000/water. This mixture was used for next step without purification.

> **Quantitative analysis was made by HPLC method according to the General Procedures*

Step 2. General procedure for redaction of the Step 1 reaction mixture

The mixture of *p*-nitrosodiphenylamine **(1)** and *p*-nitrodiphenylamine **(2)** in PEG 4000/water from *Step 1* and 0.1 g of 10% Pd/C were placed to an autoclave. After filling with hydrogen at 30 bar, the autoclave was heated at 80°C for 1 h. The autoclave was decompressed, the reaction mixture was filtered through the Schott filter (S4) and the product was isolated from the filtrate by vacuum distillation at 0.1 mBar to afforde 12.6 g (95%) of *p*-aminodiphenylamine as a brownish viscous liquid which solidified on standing.

^{1}H NMR (400 MHz, CDC_3): δ 7.19 (dd:, *J* = 7.4 and 7.9 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 7.9 Hz, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 2H), 5.41 (br. s, 1H, HN), 3.55 (br. s, 2H, NH_2); ^{13}C NMR (100 MHz, CDC3): δ 145.9,141.8, 133.6, 129.1, 122.9, 118.7, 116.1, 114.9.

*Procedure for synthesis of 2,2'-bis(1-indenyl)propane**

The 250 ml reactor with a mechanical stirrer was charged with PEG 4000 (100 g) and potassium hydroxide (14 g, 250 mmol). For dissolving of KOH, small amount of methanol (5 ml) was added and the mixture was heated to 120 °C under vigorous stirring for 20 min. The clean homogenous solution obtained was cooled to 65 °C and indene (11.6 g, 0.1 mol) was added in one portion. After one hour, acetone (2.9 g, 0.05 mol) was added dropwise and the reaction mixture was kept at this temperature overnight. After diluting with water/THF mixture (100 ml, 1:1) the resulting mixture was neutralized with the solution of HCl (6 N) giving rise to a homogenous solution. According to HPLC analysis* 12 g (55%) of 2,2'-bis(1-indenyl)propane was obtained. For isolation of the product the neutralized mixture was extracted with ether (3*50 ml), the combined extracts were dried over $CaCl_2$, passed through the short pad of silica and evaporated. The residual brown oil was crystallized from pentane and dried under vacuum.

^{1}H NMR (400 MHz, CDC_3): δ δ 1.80 (s, 6H, Me), 3.43 (br. s, 4H), 6.55 (br s, 2H,), 7.08 (p, 4H), 7.41 (dd, 4H).

** Quantitative HPLC analyses was performed using $C_{20}H_{42}$ as internal standard (calibration equation y = 0.546x [R2 = 0.999]).*

Varying of the reaction parameters

Effect of varying the PEG (Mw 600, 1000, 1280, 1500, 2000, 3400, 6000, 8000 Daltons). Condensation of aniline and nitrobenzene was performed according to *Step1* ($PhNH_2$ 60 ml; $PhNO_2$ 8.85 g; PEG 35 g; KOH 5.88 g; air flow rate 375 ml/min; pressure 60 mbar; time 2.5 h; temperature 60°C) except the PEGs of various Mw were utilized. The data obtained are shown in Figure S1 below.

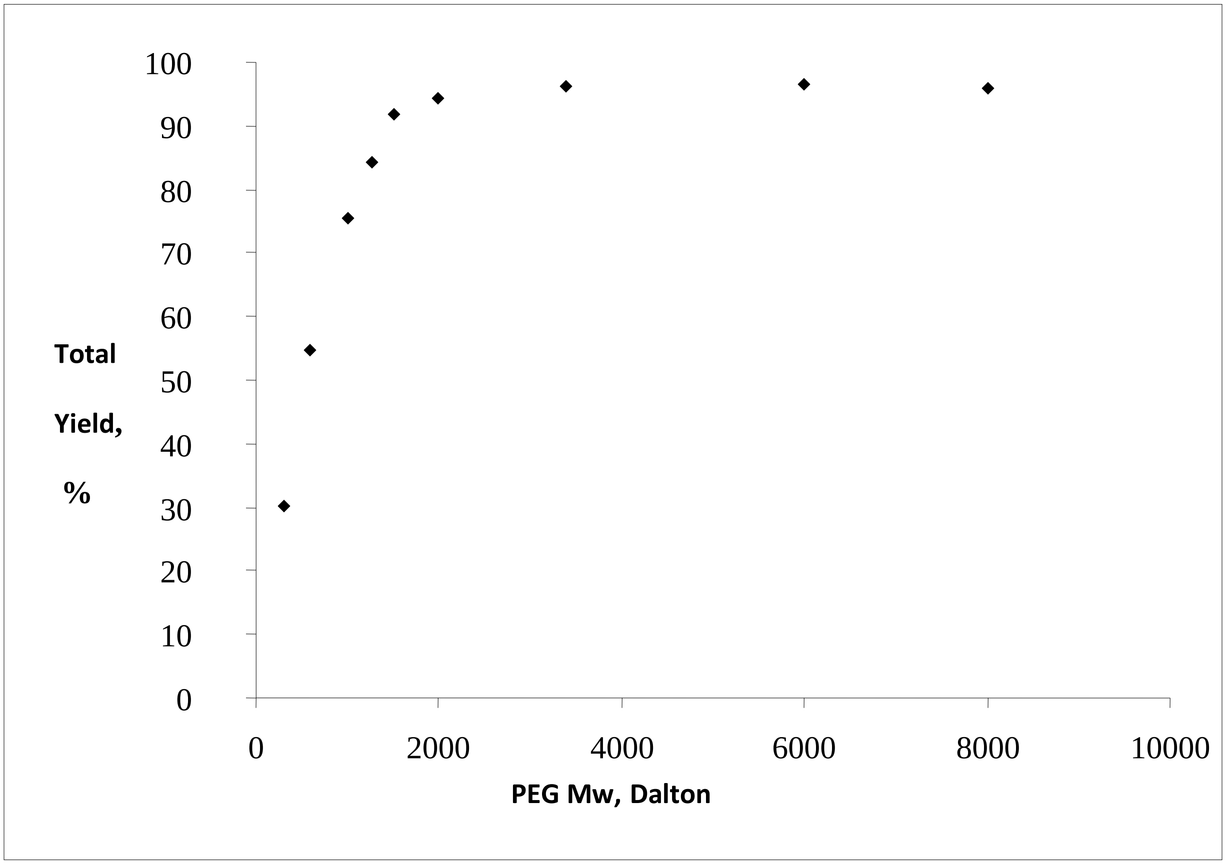

Figure S1 The dependence of total yield of the products on PEG molecular weights.

According to Figure S1, PEG with average Mw less than 1500 Dalton give rise to the low yields of the biphenylamine products, whereas PEG 2000 and higher led to almost quantitative yields of these products.

Effect of varying the PEG loading. Condensation of aniline and nitrobenzene was performed according to *Step1* ($PhNH_2$ 60 ml; $PhNO_2$ 8.85 g; KOH 5.88 g; air flow rate 375 ml/min; pressure 60 mbar; time 2.5 h; temperature 60°C) except for the PEG 4000 amounts were varied as shown in Figure 2 below.

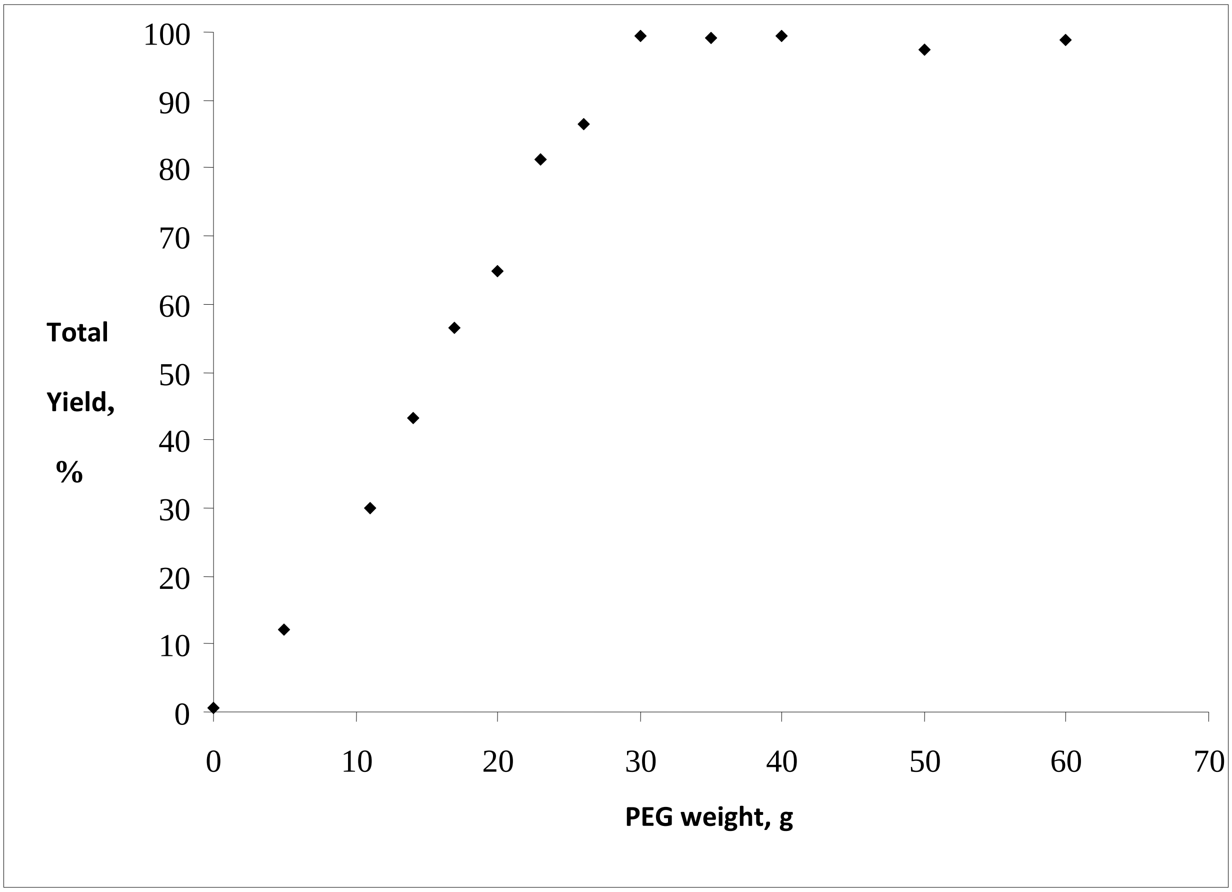

Figure S2 The dependence of total yield of the products on PEG 4000 loading.

According to Figure S2, the best result was achieved when the PEG 4000 / KOH weight ratio is equal to 5.1 or more.

Effect of varying the reaction temperature. Condensation of aniline and nitrobenzene was performed according to *Step1* ($PhNH_2$ 60 ml; $PhNO_2$ 8.85 g; PEG 35 g; KOH 5.88 g; air flow rate 375 ml/min; pressure 60 mbar; time 2.5 h) except for the temperatures having been varied as shown in Figure S3.

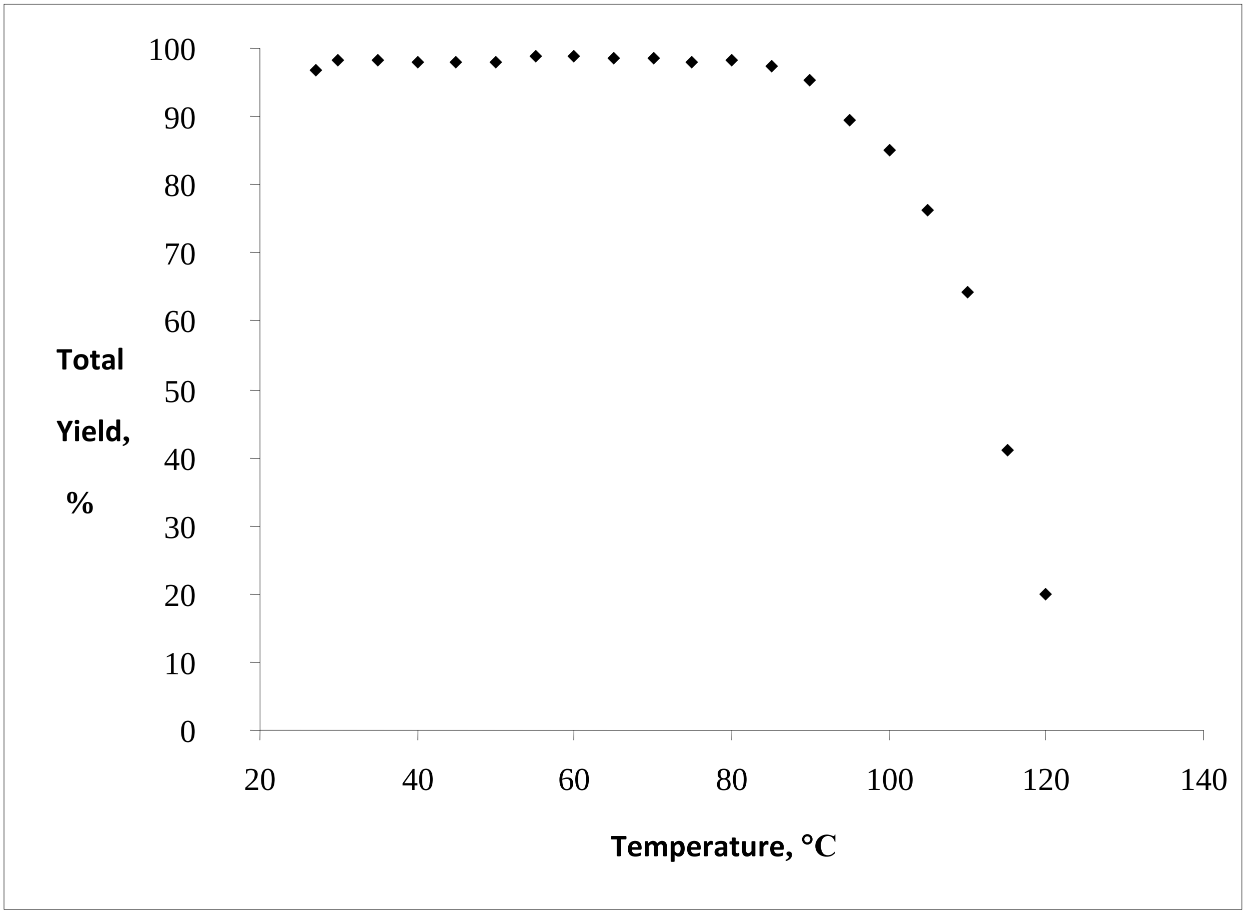

Figure S3 The dependence of total yield on process temperature.

According to Figure S3, the optimal process temperatures are in the rage of 30 to 80 °C, thus the procedure allows to archive quantitative yields even at room temperature.

NMR spectra

28 May 2016

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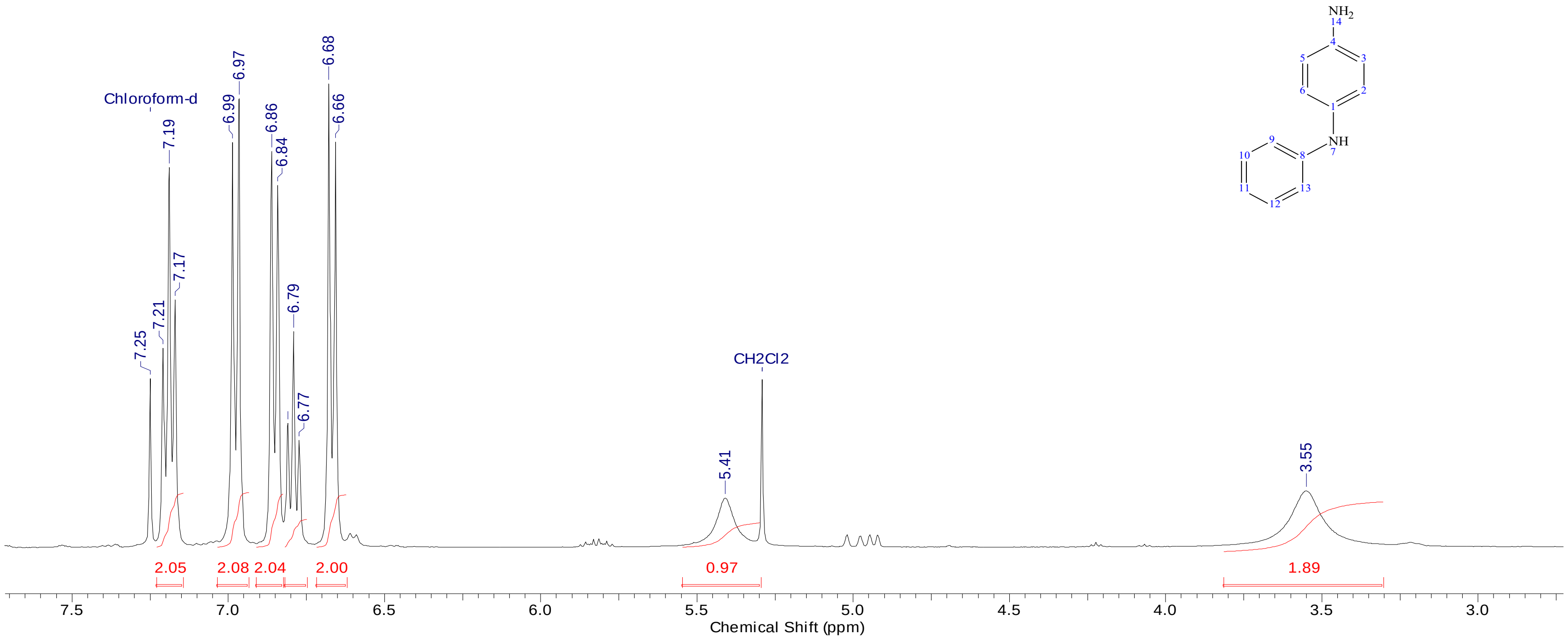
Pulse Sequence	zg30	***Solvent***	CHLOROFORM-D			***Sweep Width (Hz)***	8278.15
Temperature (degree C)	19.560						



No.	(ppm)	(Hz)	Height
1	0.89	354.4	0.1344
2	1.26	504.4	1.0000
3	1.29	516.1	0.1952
4	1.38	551.7	0.1200
5	3.55	1420.5	0.1213
6	5.41	2164.3	0.1063
7	6.66	2663.5	0.8747
8	6.68	2672.1	0.9999
9	6.77	2710.0	0.2304
10	6.79	2717.3	0.4648
11	6.81	2724.6	0.2670
12	6.84	2737.5	0.7805
13	6.86	2745.3	0.8540
14	6.97	2787.0	0.9684
15	6.99	2795.6	0.8731
16	7.17	2868.9	0.5340
17	7.19	2876.5	0.8197
18	7.21	2884.5	0.4297
19	7.25	2901.0	0.3636

No.	Annotation	(ppm)
1	CH2Cl2	5.29
2	Chloroform-d	7.25

No.	(ppm)	Value	Absolute Value
1	[5.29 .. 5.55]	0.968	2.81636e+8
2	[6.75 .. 6.82]	1.060	3.08188e+8
3	[3.30 .. 3.81]	1.891	5.49894e+8
4	[6.62 .. 6.72]	2.000	5.81678e+8
5	[6.82 .. 6.91]	2.036	5.92141e+8
6	[7.14 .. 7.23]	2.051	5.96566e+8
7	[6.93 .. 7.04]	2.080	6.04844e+8

Figure S4 A representative ^{1}H NMR spectrum of 4-ADPA **(3)** obtained by the *Step 1 and 2 of General procedure*.

20 Jul 2016

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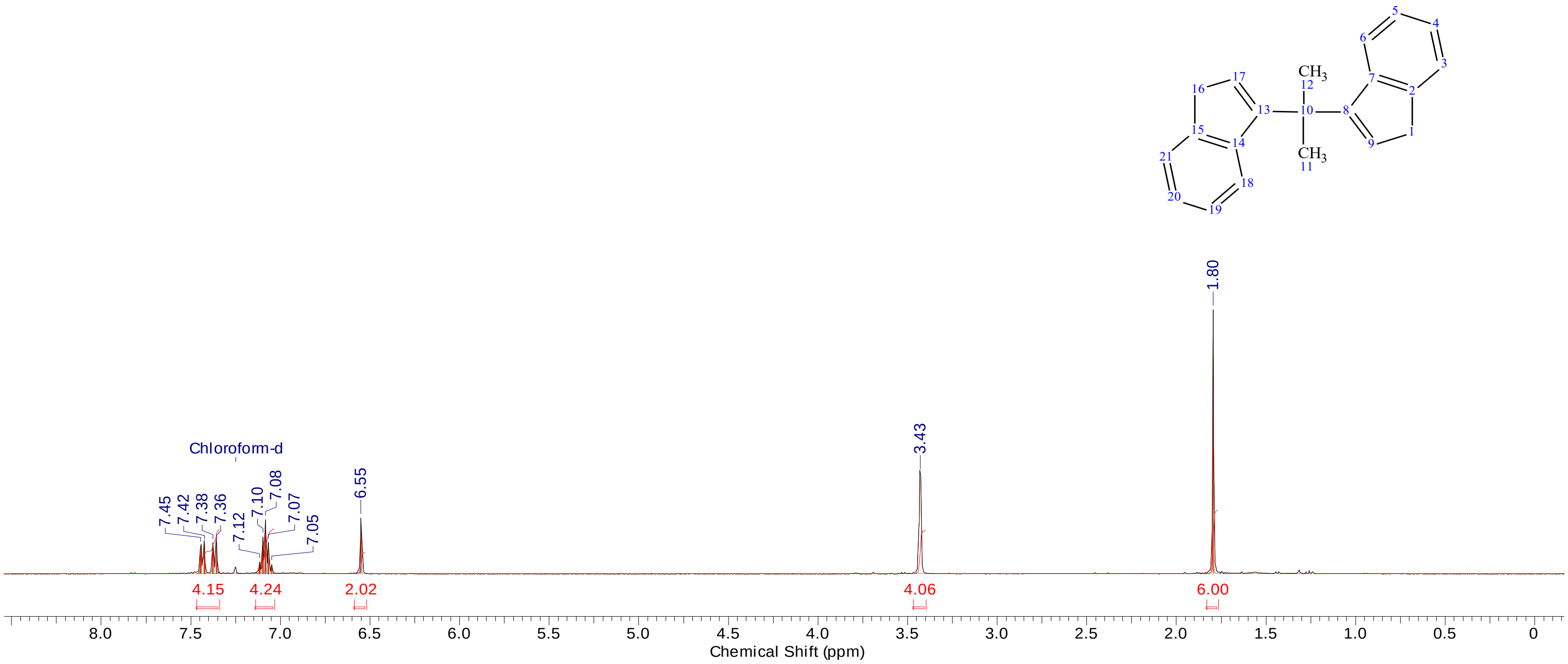
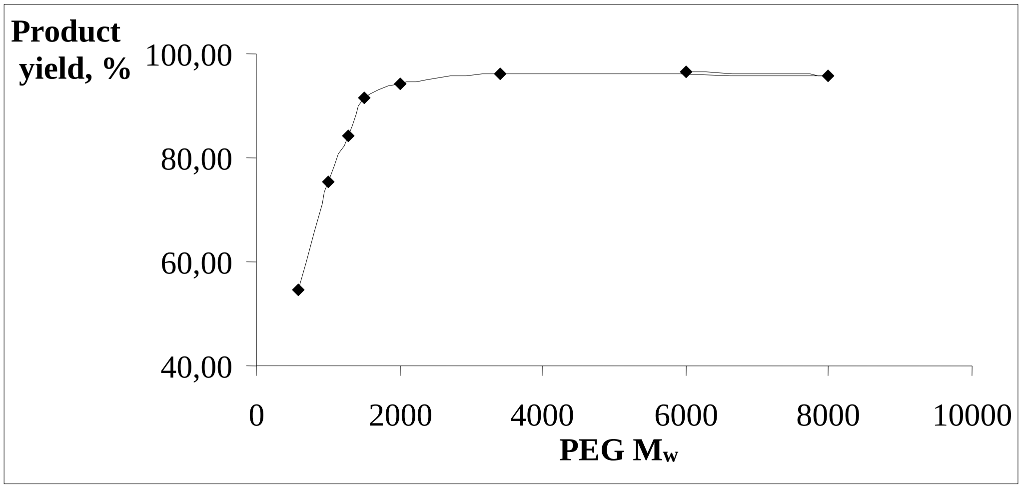
Temperature (degree C)	27.000						



No.	(ppm)	(Hz)	*(ppm)	*(Hz)	Height	*Height	*FWHH	*Area	*LF	*Function
1	1.80	718.7	1.80	718.66	1.0000	1.0000	0.70	0.92	0.50	Gauss+Lorentz
2	3.43	1372.4	-	-	0.3801	-	-	-	-	-
3	6.55	2621.0	6.55	2621.05	0.2110	0.2110	0.70	0.19	0.50	Gauss+Lorentz
4	7.05	2820.7	7.05	2820.66	0.0362	0.0362	0.70	0.03	0.50	Gauss+Lorentz
5	7.07	2828.0	7.07	2827.97	0.1188	0.1188	0.70	0.11	0.50	Gauss+Lorentz
6	7.08	2834.0	7.08	2833.96	0.2040	0.2040	0.70	0.19	0.50	Gauss+Lorentz
7	7.10	2840.1	7.10	2840.06	0.1398	0.1398	0.70	0.13	0.50	Gauss+Lorentz
8	7.12	2847.0	7.12	2847.05	0.0452	0.0452	0.70	0.04	0.50	Gauss+Lorentz
9	7.36	2943.1	7.36	2943.08	0.1150	0.1150	0.70	0.11	0.50	Gauss+Lorentz
10	7.38	2951.7	7.38	2951.73	0.1176	0.1176	0.70	0.11	0.50	Gauss+Lorentz
11	7.42	2970.6	7.42	2970.58	0.1142	0.1142	0.70	0.11	0.50	Gauss+Lorentz
12	7.45	2979.1	7.45	2979.12	0.1060	0.1060	0.70	0.10	0.50	Gauss+Lorentz

No.	Annotation	(ppm)
1	Chloroform-d	7.25

Figure S5 ^{1}H NMR spectrum of 2,2'-bis(1-indenyl)propane.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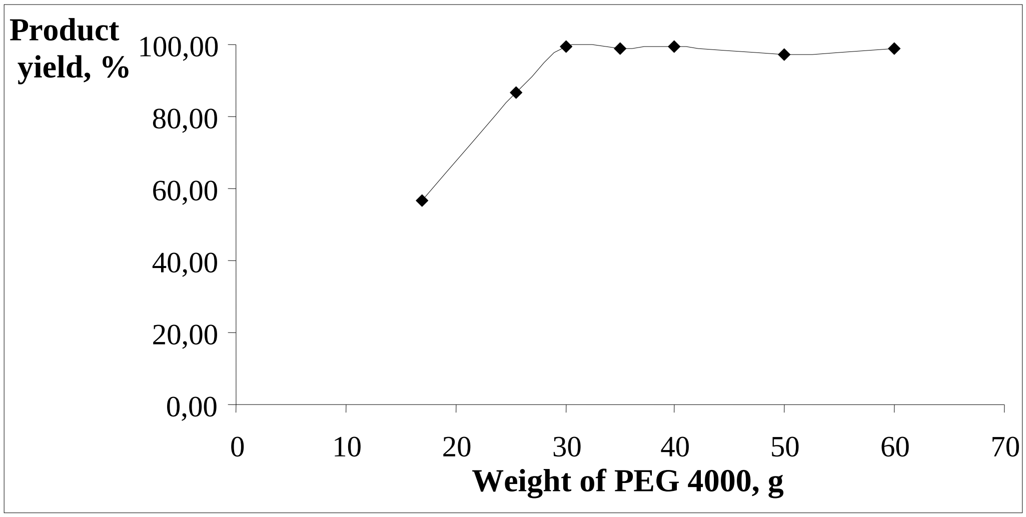
4000
6000
8000
10000
PEG Mw


Product yield, %
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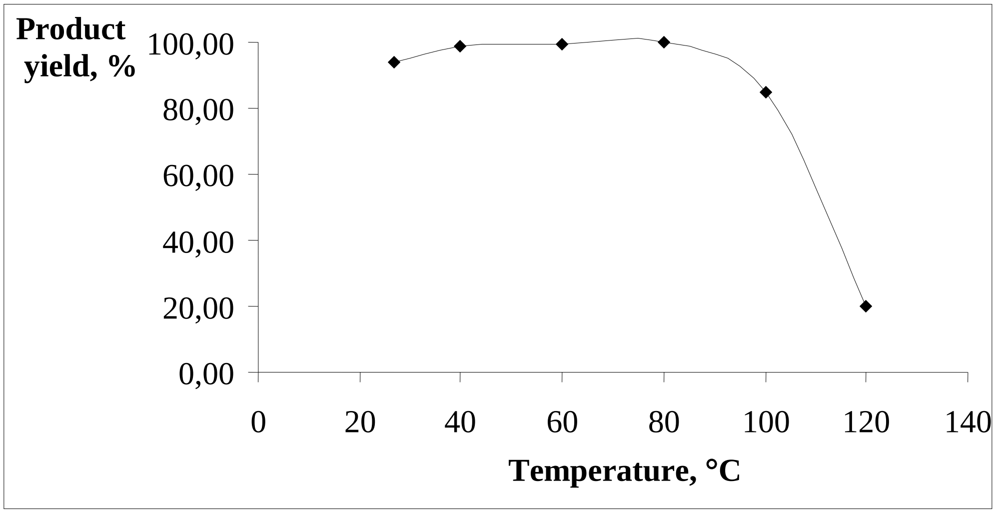
40,00
20,00
0,00
0
10
20
30
40
50
60
70
Weight of PEG 4000, g


Product yield, %
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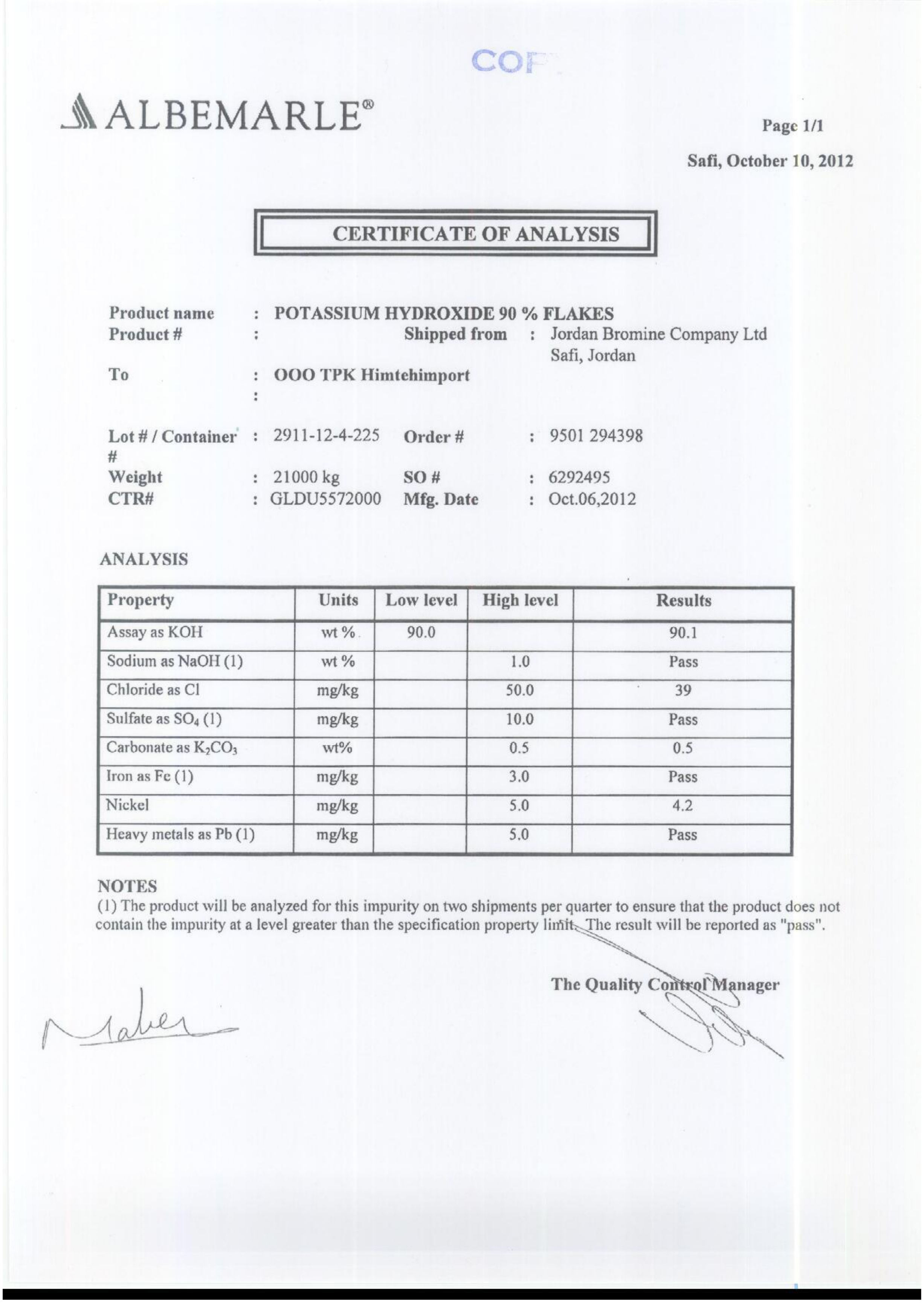
20,00
0,00
0
20
40
60
80
100
120
140
Temperature, °C



COP

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Page 1/1

Safi, October 10, 2012

CERTIFICATE OF ANALYSIS

Product name : **POTASSIUM HYDROXIDE 90 % FLAKES**
Product # : **Shipped from** : Jordan Bromine Company Ltd
Safi, Jordan
To : **OOO TPK Himtehimport**
:

Lot # / Container # : 2911-12-4-225 **Order #** : 9501 294398
Weight : 21000 kg **SO #** : 6292495
CTR# : GLDU5572000 **Mfg. Date** : Oct.06,2012

ANALYSIS

Property	Units	Low level	High level	Results
Assay as KOH	wt %	90.0		90.1
Sodium as NaOH (1)	wt %		1.0	Pass
Chloride as Cl	mg/kg		50.0	39
Sulfate as SO_4 (1)	mg/kg		10.0	Pass
Carbonate as K_2CO_3	wt%		0.5	0.5
Iron as Fe (1)	mg/kg		3.0	Pass
Nickel	mg/kg		5.0	4.2
Heavy metals as Pb (1)	mg/kg		5.0	Pass

NOTES

(1) The product will be analyzed for this impurity on two shipments per quarter to ensure that the product does not contain the impurity at a level greater than the specification property limit. The result will be reported as "pass".

The Quality Control Manager

Maher