Rapid and facile solvent-free mechanosynthesis in a cell lysis mill: preparation and mechanochemical complexation of aminobenzoquinones

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SUPPORTING INFORMATION

1. Materials and Methods

Chemicals: 4,6-Diaminoresorcinol dihydrochloride, *n*-butylamine, dodecylamine, octadecylamine and deuterated chloroform were obtained from Aldrich. 1,4-Benzoquinone was obtained from American Chemicals. Chloroform, hexanes, ethanol and methanol were obtained from Fisher Scientific. Deuterated DMSO was obtained from Cambridge Isotope Laboratories, Inc. Toluene was obtained from J.T. Baker. Nickel(II) acetate tetrahydrate ($Ni(OAc)_2 \bullet 4H_2O$) was obtained from BDH Chemicals. Nickel(II) hydroxide ($Ni(OH)_2$) was obtained from Research Organic/Inorganic Chemical Corp. Melting points (m.p.) were recorded with a capillary melting point apparatus (Thomas Hoover). The recorded R_f values were determined by a standard thin-layer chromatography (TLC) procedure: 0.25 mm silica gel plates (Aldrich).

NMR: ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Varian 500 spectrometer. The residual proton signals of the deuterated solvents were used as internal standards ($CDCl_3$: δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.0 ppm; DMSO: δ (^{1}H) 2.48 ppm, δ (^{13}C) 40.0 ppm). The following notation is used for the ^{1}H NMR splitting patterns: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad signal (br).

MS: For both *meta* and *para* compounds mass spectrometric analysis was performed using a Waters Micromass, Quattro LC triple quadrupole mass spectrometer (Waters, Montreal, PQ, Canada). The instrument was operated using an ESI (electrospray ionization) source by direct injection with a syringe pump (50 μL syringe; flow rate: 1 μL/min). The MS instrument was operated in the positive mode (ES+) and the data acquisition/analysis was carried out using Masslynx software version 4.01. Source working conditions were as follows: cone voltage: 20 V, Capillary voltage: 3.3 V, source temperature: 90 °C, desolvation temperature: 100 °C, desolvation gas flow rate: 220 L/hr, nitrogen: (99.9% purity). Mass spectrometric analysis of individual compounds: The aminobenzoquinone derivatives (*ca.* 0.1 mg) were dissolved in acetonitrile/water (1:1; 100 mL). Prior to MS analysis, 1 mL of this solution was further diluted into acetonitrile/water (1:1; 10 mL) and formic acid (10 μL) was added. For (**C18*m***)$_2$Ni, mass spectrometry measurements were performed using a Bruker Ultraflex MALDI TOF/TOF Mass Spectrometer. MALDI was used as the ionization method, with dithranol as matrix, in reflector mode. The protonated molecular ion $[M]^+$ was used for empirical formula confirmation.

2. Synthesis and characterization

General Methods for synthesizing *meta* (*m*) compounds

Method A$_m$: Conventional solvent synthesis[1]

In a round-bottom flask, a total mass of *ca.* 0.2 g of 4,6-diaminoresorcinol dihydrochloride and 4-7 equiv. of various primary alkylamines, RNH_2, were mixed in 10 mL of solvent. The mixture was left to stir for two hours and subsequently dried under reduced pressure. The crude product was dissolved in a minimum amount of chloroform, insoluble solids were filtered out and the filtrate was purified by centrifugal thin-layer chromatography on silica using 96:4 chloroform:methanol as eluent.

Method B_m: Cell lysis milling

In a 2 mL screw cap Eppendorf® tube, a total mass of *ca.* 0.1 g 4,6-diaminoresorcinol dihydrochloride and 4-7 equiv. of various primary alkylamines, RNH_2, were combined with sufficient ceramic beads (0.8 mm diameter) to fill the lysis tube to 3/4 of its height. The tube was then shaken at 6.0 m/s using a cell lysis mill (FastPrep®-24; MP-Biomedicals, NY, USA; www.mpbio.com) for 10 shaking cycles (1 minute shaking with a 5 minute instrument cooling period - 10 shaking cycles is equivalent to 10 minutes shaking time and 1 hour total time). The crude product was purified by centrifugal thin-layer chromatography on silica using 96:4 chloroform:methanol as eluent.

Method C_m: Ball milling

In a 10 mL steel milling jar with two stainless steel balls of 7 mm diameter, a total mass of *ca.* 0.2 g 4,6-diaminoresorcinol dihydrochloride and 4-7 equiv. of various primary alkylamines, RNH_2, were added. The reaction mixture was ground for a period of 60 minutes in a Retsch MM200 ball mill operating at a frequency of 30 Hz. The crude product was purified by centrifugal thin-layer chromatography on silica using 96:4 chloroform:methanol as eluent.

Method D_m: Melt

In a 5 mL glass vial with a stir bar, a total mass of *ca.* 0.4 g 4,6-diaminoresorcinol dihydrochloride and 7-10 equiv. of various primary alkylamines, RNH_2, were combined and heated with stirring for 10 minutes at a temperature slightly higher than the melting point of the alkylamine. The crude product was purified by centrifugal thin-layer chromatography on silica using 96:4 chloroform:methanol as eluent.

General Methods for synthesizing *para* (*p*) compounds

Method A_p: Conventional solvent synthesis[2,3]

In a round-bottom flask, a total mass of *ca.* 0.2 g 1,4-benzoquinone and various primary alkylamines, RNH_2, with a molar ratio of 3:2 were mixed in 10 mL of ethanol. The mixture was left to stir for five hours and the solvent was subsequently removed under reduced pressure. The crude product was dissolved in a minimum amount of chloroform and purified by centrifugal thin-layer chromatography on silica using 99.5:0.5 chloroform:methanol as eluent.

Method B_p: Cell lysis milling

In a 2 mL screw cap Eppendorf® tube, a total mass of *ca.* 0.1 g 1,4-benzoquinone and various primary alkylamines, RNH_2, with a molar ratio of 3:2 were combined with sufficient ceramic beads (0.8 mm diameter) to fill the lysis tube to 3/4 of its height. The tube was then shaken at 6.0 m/s using a cell lysis apparatus (FastPrep®-24; MP-Biomedicals, NY, USA; www.mpbio.com) for 10 shaking cycles (1 minute shaking with a 5 minute instrument cooling period - 10 shaking cycles is equivalent to 10 minutes shaking time and 1 hour total time). The crude product was dissolved in a minimum amount of chloroform and purified by centrifugal thin-layer chromatography on silica using 99.5:0.5 chloroform:methanol as eluent.

Method C_p: Ball milling

In a 10 mL steel milling jar with two stainless steel balls of 7 mm diameter, a total mass of *ca.* 0.2 g 1,4-benzoquinone and various primary alkylamines, RNH_2, with a molar ratio of 3:2 were added. The reaction mixture was ground for a period of 7 minutes in a Retsch MM200 ball mill operating at a frequency of 30 Hz. The crude product was dissolved in a minimum amount of chloroform and purified by centrifugal thin-layer chromatography on silica using 99.5:0.5 chloroform:methanol as eluent.

Method D_p: Melt

In a 5 mL glass vial with a stir bar, a total mass of *ca.* 0.4 g 1,4-benzoquinone and 0.7 equiv. various primary alkylamines, RNH_2, were added and heated for 5 minutes with stirring to a temperature slightly higher than the melting point of the alkylamine. The crude product was dissolved in a minimum amount of chloroform and purified by centrifugal thin-layer chromatography on silica using 99.5:0.5 chloroform:methanol as eluent.

4,6-diamino-*m*-quinone (C0*m*)[1]:

4,6-Diaminoresorcinol dihydrochloride (30.9 mg; 0.145 mmol) was dissolved in methanol (4 mL), and one drop of concentrated ammonium hydroxide was added to the stirred solution. The mixture was left to stir for *ca*. one day. The resulting dark purple precipitate was isolated by filtration, washed with water, and then dried in air. The air-dried product was subsequently dried under reduced pressure to afford the title compound (18.2 mg; 0.132 mmol; 91%; dark red). m.p. > 250 °C; R_f 0 (90/10 $CHCl_3$/MeOH); ^{1}H NMR (500 MHz, DMSO-D_6 at 21°C) δ = 4.89 (s, 1H, N-C-C-*H*), 5.60 (s, 1H, O-C-C-*H*), 8.38 (s, 2H, NH_2), 9.15 (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-D_6 at 21°C): δ = 86.7 (N-C-*C*), 98.4 (O-C-*C*), 160.5 (N-*C*), 173.0 (O-*C*).

4,6-di(butylamino)-*m*-quinone (C4*m*)[1]:

Conventional solvent synthesis

a) General Method A_m was followed using methanol (10 mL), 4,6-diaminoresorcinol dihydrochloride (84.9 mg; 0.40 mmol) and *n*-butylamine (0.16 mL; 119 mg; 1.63 mmol; 4 equiv.) to provide the title compound (79.1 mg; 0.32 mmol; 79%).

b) General Method A_m was followed using methanol (10 mL), 4,6-diaminoresorcinol dihydrochloride (60.0 mg; 0.28 mmol) and *n*-butylamine (0.19 mL; 141 mg; 1.93 mmol; 7 equiv.) to provide the title compound (60.1 mg; 0.24 mmol; 88%).

Lysis milling

a) General method B_m was followed using 4,6-diaminoresorcinol dihydrochloride (44.7 mg; 0.21 mmol) and *n*-butylamine (0.089 mL; 62.3 mg; 0.85 mmol; 4 equiv.) to provide the title compound (43.9 mg; 0.18 mmol; 83%).

b) General method B_m was followed using 4,6-diaminoresorcinol dihydrochloride (27.7 mg; 0.13 mmol) and *n*-butylamine (0.095 mL; 70.3 mg; 0.96 mmol; 7 equiv.) to provide the title compound (28.2 mg; 0.11 mmol; 86%).

Ball milling

a) General method C_m was followed using 4,6-diaminoresorcinol dihydrochloride (83.3 mg; 0.39 mmol) and *n*-butylamine (0.156 mL; 115.8 mg; 1.58 mmol; 4 equiv.) to provide the title compound (78.4 mg; 0.31 mmol; 80%).

b) General method C_m was followed using 4,6-diaminoresorcinol dihydrochloride (62.0 mg; 0.29 mmol) and *n*-butylamine (0.202 mL; 150 mg; 2.1 mmol; 7 equiv.) to provide the title compound (65.2 mg; 0.26 mmol; 89%).

Melt

General method D_m was followed using 4,6-diaminoresorcinol dihydrochloride (89.6 mg; 0.42 mmol) and *n*-butylamine (0.418 mL; 310 mg; 4.2 mmol; 10 equiv.) to provide the title compound (97.3 mg; 0.39 mmol; 92%)

m.p. 156-157°C; R_f 0.25 (98/2 $CHCl_3$/MeOH); purple powder; ^{1}H NMR (500 MHz, $CDCl_3$ at 21°C) δ = 0.99 (t, ^3J= 7.0 Hz, 6H, CH_2-CH_3), 1.44 (sextet, ^3J= 7.5 Hz, 4H, CH_2-CH_2-CH_3), 1.73 (quintet, ^3J= 7.0 Hz, 4H, NH-CH_2-CH_2), 3.38 (q, ^3J= 6.5 Hz, 4H, NH-CH_2), 5.14 (s, 1H, NH-C-C*H*), 5.45 (s, 1H, O-C-C*H*), 8.26 (br, 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$ at 21°C) δ = 13.6 (*C*H_3-CH_2), 20.1 (*C*H_2CH_3), 30.2 (NH-CH_2-*C*H_2), 43.0 (NH-*C*H_2-CH_2), 80.6 (NH-C-*C*H), 99.0 (O-C-*C*H), 156.6 (NH-*C*), 172.4 (*C*-O).

4,6-di(dodecylamino)-*m*-quinone (**C12*m***):

Conventional solvent synthesis

a) General Method A_m was followed using ethanol (10 mL), 4,6-diaminoresorcinol dihydrochloride (45.0 mg; 0.21 mmol) and dodecylamine (158.7 mg; 0.86 mmol; 4 equiv.) to provide the title compound (70.3 mg; 0.15 mmol; 70%).

b) General Method A_m was followed using ethanol (10 mL), 4,6-diaminoresorcinol dihydrochloride (28.2 mg; 0.13 mmol) and dodecylamine (176.0 mg; 0.95 mmol; 7 equiv.) to provide the title compound (46.6 mg; 0.10 mmol; 74%).

Lysis milling

a) General method B_m was followed using 4,6-diaminoresorcinol dihydrochloride (22.5 mg; 0.11 mmol) and dodecylamine (80.0 mg; 0.43 mmol; 4 equiv.) to provide the title compound (39.9 mg; 0.08 mmol; 79%)

b) General method B_m was followed using 4,6-diaminoresorcinol dihydrochloride (13.9 mg; 0.07 mmol) and dodecylamine (88.3 mg; 0.48 mmol; 7 equiv.) to provide the title compound (22.6 mg; 0.06 mmol; 85%)

Ball milling

a) General method C_m was followed using 4,6-diaminoresorcinol dihydrochloride (44.2 mg; 0.21 mmol) and dodecylamine (156.3 mg; 0.84 mmol; 4 equiv.) to provide the title compound (80.1 mg; 0.17 mmol; 81%).

b) General method C_m was followed using 4,6-diaminoresorcinol dihydrochloride (27.9 mg; 0.13 mmol) and dodecylamine (173.6 mg; 0.94 mmol; 7 equiv.) to provide the title compound (53.7 mg; 0.11 mmol; 86%).

Melt

General method D_m was followed using 4,6-diaminoresorcinol dihydrochloride (50.3 mg; 0.24 mmol) and dodecylamine (361.9 mg; 1.95 mmol; 8 equiv.) to provide the title compound (94.7 mg; 0.20 mmol; 84%). In addition to following general method D_m, the two starting materials were premixed using a mortar and pestle before transferring to a glass vial.

m.p. 95-96 °C; R_f 0.45 (98/2 $CHCl_3$/MeOH); purple green powder, pink power if wet, red if in solution ^{1}H NMR (500 MHz, $CDCl_3$ at 21°C) δ = 0.88 (t, ^3J= 7.0 Hz, 6H, CH_2-CH_3), 1.22-1.50 (m, 36H, CH_2-CH_2), 1.74 (quintet, ^3J= 7.0 Hz, 4H, NH-CH_2-CH_2), 3.36 (q, ^3J= 6.5 Hz, 4H, NH-CH_2), 5.12 (s, 1H, NH-C-C*H*), 5.46 (s, 1H, O-C-C*H*), 8.24 (br, 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$ at 21°C) δ = 14.1 (*C*H_3-CH_2), 22.6 (*C*H_2CH_3), 26.9, 27.5, 28.6, 29.73, 29.74, 29.8, 29.9, 32.0 (*C*H_2CH_2), 43.9 (NH-*C*H_2-CH_2), 80.3 (NH-C-*C*H), 98.8 (O-C-*C*H), 156.4 (NH-*C*), 172.2 (*C*-O), MS (Triple Quad-ESI): m/z: 475.40 $[M+H]^+$, calcd $[M+H]^+$: 475.43

4,6-di(octadecylamino)-*m*-quinone (**C18*m***)[4]:

Conventional solvent synthesis

a) General Method A_m was followed using ethanol (10 mL), 4,6-diaminoresorcinol dihydrochloride (31.6 mg; 0.15 mmol) and octadecylamine (161.9 mg; 0.60 mmol, 4 equiv.) to provide the title compound (71.7 mg; 0.11 mmol; 75%).

b) General Method A_m was followed using ethanol (10 mL), 4,6-diaminoresorcinol dihydrochloride (20.1 mg; 0.09 mmol) and octadecylamine (183.3 mg; 0.68 mmol, 7 equiv.) to provide the title compound (48.7 mg; 0.08 mmol; 80%).

Lysis milling

a) General method B_m was followed using 4,6-diaminoresorcinol dihydrochloride (15.7 mg; 0.07 mmol) and octadecylamine (82.5 mg; 0.31 mmol; 4 equiv.) to provide the title compound (33.2 mg; 0.05 mmol; 70%)

b) General method B_m was followed using 4,6-diaminoresorcinol dihydrochloride (9.9 mg; 0.05 mmol) and octadecylamine (93 mg; 0.35 mmol; 7 equiv.) to provide the title compound (27.0 mg; 0.04 mmol; 90%)

Ball milling

a) General method C_m was followed using 4,6-diaminoresorcinol dihydrochloride (82.8 mg; 0.15 mmol) and octadecylamine (168.5 mg; 0.63 mmol; 4 equiv.) to provide the title compound (82.8 mg; 0.13 mmol; 83%)

b) General method C_m was followed using 4,6-diaminoresorcinol dihydrochloride (20.1 mg; 0.09 mmol) and octadecylamine (181.5 mg; 0.67 mmol; 7 equiv.) to provide the title compound (78.1 mg; 0.08 mmol; 87%)

Melt

General method D_m was followed using 4,6-diaminoresorcinol dihydrochloride (40.1 mg; 0.19 mmol) and octadecylamine (358.6 mg; 1.33 mmol; 7 equiv.) to provide the title compound (83.9 mg; 0.13 mmol; 69%). In addition to following general method D_m, the two starting materials were premixed using a mortar and pestle before transferring to a glass vial.

m.p. 99-101°C; R_f 0.5 (98/2 $CHCl_3$/MeOH); purple green powder or red crystal; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, ^3J= 7.0 Hz, 6H, CH_3), 1.25-1.28 (m, 56H, CH_2-CH_2-CH_2), 1.73 (quintet, ^3J= 7.3 Hz, 4H, NH-CH_2-CH_2), 3.37 (q, ^3J= 6.7 Hz, 4H, NH-CH_2), 5.13 (s, 1H, NH-C-C*H*), 5.44 (s, 1H, O-C-C*H*), 8.32 (br, 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6, 26.9, 28.3, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 43.3, 80.5 (N-C-*C*), 98.8 (O-C-*C*), 156.6 (N-*C*), 172.3 (O-*C*); MS (Triple Quad-ESI): m/z: 643.65 $[M+H]^+$ calcd $[M+H]^+$: 643.61.

Bis[4-(octadecylamino)-2-(octadecylimino)-5-oxo-1,4-cyclohexadienolato]nickel ((**C18*m***)$_2$Ni): *Conventional solvent synthesis*[5]

a) **C18*m*** (80.0 mg; 0.12 mmol) was dissolved in toluene (10.0 mL) with nickel(II) acetate tetrahydrate ($Ni(OAc)_2.4H_2O$; 28.1 mg; 0.11 mmol). The mixture was left to stir under reflux for 12 hours. After cooling the solution, the resulting precipitate, purple with a metallic lustre, was isolated by filtering through a Pyrex® glass Buchner funnel with a medium porosity fritted disc (10-15 μm) and washed with cold chloroform (to remove starting material, **C18*m***), hot water (to remove starting material $Ni(OAc)_2$) and dried in air. The crude product (*ca.* 90% pure) was further purified by using hot chloroform to transfer the compound from the fritted filter to a separatory funnel. Additional chloroform was added to adjust the volume of chloroform to about 40 mL, and the separatory funnel was capped to prevent solvent evaporation. (**C18*m***)$_2$Ni slowly crystallized out of the solution, and due to the lower density of (**C18*m***)$_2$Ni with respect to the chloroform, floated to the top of the solution as a purple precipitate. After one day the lower phase, a red solution containing the starting material **C18*m***, was drained, and another 40 mL of fresh hot chloroform was added to redissolve the (**C18*m***)$_2$Ni. This process was repeated 3 to 4 times until the lower phase was only light pink in color. The solvent was drained and the final metallic lustre purple solid was dried under reduced pressure to give the title compound (57.5 mg; 0.04 mmol; 69%). Recrystallization from various solvents was attempted but gave lower purity (95%). Chromatography (the Ni complex does not move on Si, Al and cellulose plates) and soxhlet extraction (the Ni complex dissolves in most hot solvents) were unsuccessful purification methods.

b) **C18*m*** (88.2 mg; 0.14 mmol) was dissolved in toluene (10.0 mL) with nickel(II) hydroxide ($Ni(OH)_2$; 15.0 mg; 0.14 mmol). The mixture was left to stir under reflux for 12 hours. After cooling the solution, the resulting precipitate, purple with a metallic lustre, was isolated by filtering through a Pyrex® glass Buchner funnel with a medium porosity fritted disc (10-15 μm) and washed with cold chloroform (to remove starting material, **C18*m***), and dried in air. The crude product (*ca.* 90% pure) was further purified by using hot chloroform to transfer the compound from the fritted filter to a separatory funnel, leaving $Ni(OH)_2$ behind, and following the same purification procedure described above to give the title compound (9.5 mg; 0.007 mmol; 10%).

Lysis milling

a) In a 2 mL screw cap Eppendorf® tube, **C18*m*** (71.0 mg; 0.11 mmol) and nickel(II) acetate tetrahydrate ($Ni(OAc)_2.4H_2O$; 27.1 mg; 0.11 mmol; 1 equiv.) were combined with sufficient ceramic beads (0.8 mm diameter) to fill the lysis tube to 3/4 of its height. The tube was then shaken at 6.0 m/s using a cell lysis mill (FastPrep®-24; MP-Biomedicals, NY, USA; www.mpbio.com) for 20 shaking cycles (1 minute shaking with a 5 minute instrument cooling period - 20 shaking cycles equal to 20 minutes shaking time and 2 hour total time). The crude product was dissolved in hot chloroform. After cooling the solution, the resulting precipitate, purple color with metallic lustre, was isolated by filtering through a Pyrex® glass Buchner funnel with medium porosity fritted disc (10-15 μm) the same purification procedure as described in the conventional solvent synthesis was followed (57.5 mg; 0.05 mmol; 85%).

b) In a 2 mL screw cap Eppendorf® tube, **C18*m*** (81.9 mg; 0.13 mmol) and nickel(II) hydroxide ($Ni(OH)_2$; 13.9 mg; 0.13 mmol; 1 equiv.) were combined with sufficient ceramic beads (0.8 mm diameter) to fill the lysis tube to 3/4 of its height. The tube was then shaken at 6.0 m/s using a commercial cell disruptor or a lysis mill (FastPrep®-24; MP-Biomedicals, NY, USA; www.mpbio.com) for 20 shaking cycles (1 minute shaking with a 5 minute instrument cooling period - 20 shaking cycles is equivalent to 20 minutes shaking time and 2 hour total time). The crude product was dissolved in hot chloroform. After cooling down the solution, the resulting precipitate, purple with a metallic lustre, was isolated by filtering through a Pyrex® glass Buchner funnel with a medium porosity fritted disc (10-15 μm). The same purification procedure as described in the conventional solvent synthesis was followed to give the title compound (68.5 mg; 0.05 mmol; 80%).

Ball milling

a) In a 10 mL steel milling jar with two stainless steel balls of 7 mm diameter, **C18*m*** (72.8 mg; 0.11 mmol) and nickel(II) acetate tetrahydrate ($Ni(OAc)_2.4H_2O$; 27.5 mg; 0.11 mmol; 1 equiv.) were added. The reaction mixture was ground for a period of 120 minutes in a Retsch MM200 ball mill operating at a frequency of 30 Hz. The crude product was dissolved in hot chloroform. After cooling the solution, the resulting precipitate, purple with a metallic lustre, was isolated by filtering through a Pyrex® glass Buchner funnel with a medium porosity fritted disc (10-15 µm). The same purification procedure as described in the conventional solvent synthesis was followed to give the title compound (54.1 mg; 0.04 mmol; 71%).

b) In a 10 mL steel milling jar with two stainless steel balls of 7 mm diameter, **C18*m*** (83.3 mg; 0.13 mmol) and nickel(II) hydroxide ($Ni(OH)_2$; 14.1 mg; 0.13 mmol; 1 equiv.) were added. The reaction mixture was ground for a period of 120 minutes in a Retsch MM200 ball mill operating at a frequency of 30 Hz. The crude product was dissolved in hot chloroform. After cooling the solution, the resulting precipitate, purple with a metallic lustre, was isolated by filtering through a Pyrex® glass Buchner funnel with a medium porosity fritted disc (10-15 µm). The same purification procedure as described in the conventional solvent synthesis was followed to give the title compound (61.3 mg; 0.05 mmol; 70%).

m.p. > 200 °C; R_f 0 (98/2 $CHCl_3$/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$ at 45°C) δ 0.88 (t, ^3J= 7.0 Hz, 12H, CH_3), 1.20-1.65 (m, 128H, CH_2-CH_2-CH_3), 2.84 (br t, ^3J= 7.3 Hz, 4H, NH-CH_2), 3.07 (q, ^3J= 6.7 Hz, 4H, NH-CH_2), 5.02 (s, 2H, NH-C-C*H*), 5.22 (s, 2H, O-C-C*H*), 6.26 (br t, 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$ at 45°C) δ = 14.1, 22.7 (CH_3-CH_2), 27.1, 27.4 (CH3-*C*H2), 28.4, 29.33, 29.39, 29.40, 29.47, 29.54, 29.62, 29.66, 29.69, 29.72, 29.73, 29.75, 29.78, 29.9, 32.0 (CH_2CH_2), 42.7, 47.7 (NH-CH_2), 83.3 (H*C*=C), 102.6(H*C*=C), 146.7 (C-N), 167.3 (*C*-O), 180.3 (C=N), 180.6 (*C*=O); MS (MALDI): m/z: 1342.51 $[M+H]^+$ calcd $[M+H]^+$: 1342.14

2,5-di(butylamino)-1,4-quinone (C4*p*)[3]:

Conventional solvent synthesis

General method A_p was followed using 1,4-benzoquinone (141 mg; 1.3 mmol) and *n*-butylamine (0.091 mL, 64 mg; 0.88 mmol) with a molar ratio of 3:2 to provide the title compound (35.3 mg; 0.14 mmol; 32%).

Lysis milling

General method B_p was followed using 1,4-benzoquinone (70.1 mg, 0.65 mmol) and *n*-butylamine (0.044 mL, 32.7 mg; 0.45 mmol) with a molar ratio of 3:2 to provide the title compound (14.9 mg; 0.06 mmol; 27%).

Ball milling

General method C_p was followed using 1,4-benzoquinone (139 mg; 1.3 mmol) and *n*-butylamine (0.09 mL, 64 mg; 0.87 mmol) with a molar ratio of 3:2 to provide the title compound (270.0 mg; 0.11 mmol; 25%).

Melt

General method D_p was followed using 1,4-benzoquinone (275.9 mg, 2.6 mmol) and *n*-butylamine (0.171 ml, 126 mg; 1.7 mmol) with a molar ratio of 3:2 at room temperature to provide the title compound (44.1 mg; 0.18 mmol; 20%).

Following the general methods, the title compound (bright orange) was obtained after purification using 99.5:0.5 chloroform:methanol as eluent. m.p. 155-157°C; R_f 0.7 (98/2 $CHCl_3$/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$ at 21°C) δ = 0.88 (t, ^3J= 7.0 Hz, 6H, CH_2-CH_3), 1.34 (sextet, ^3J= 7.5 Hz, 4H, CH_2-CH_2-CH_3), 1.57 (quintet, ^3J= 7.0 Hz, 4H, NH-CH_2-CH_2), 3.09 (q, ^3J= 6.5 Hz, 4H, NH-CH_2), 5.24 (s, 2H, C-C*H*-C), 6.55 (br t, ^3J= 5.5 Hz 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$ at 21°C) δ = 13.6 (CH_3-CH_2), 20.1 (CH_2-CH_3), 30.2 (NH-CH_2-CH_2), 42.3 (NH-CH_2-CH_2), 92.6 (*C*H=C-NH), 151.4 (CH=*C*-NH), 178.1 (*C*=O).

2,5-di(dodecylamino)1,4-quinone (C12*p*)[6]:

Conventional solvent synthesis

General method A_p was followed using 1,4-benzoquinone (92.1 mg; 0.85 mmol) and dodecylamine (106.3 mg; 0.57 mmol) with a molar ratio of 3:2 to provide the title compound (39.5 mg; 0.08 mmol; 29%).

Lysis milling

General method B_p was followed using 1,4-benzoquinone (45.3 mg, 0.42 mmol) and dodecylamine (51.8 mg; 0.28 mmol) with a molar ratio of 3:2 to provide the title compound (20.2 mg; 0.04 mmol; 30%).

Ball milling

General method C_p was followed using 1,4-benzoquinone (91.2 mg; 0.84 mmol) and dodecylamine (105.7 mg; 0.57 mmol) with a molar ratio of 3:2 to provide the title compound (43.8 mg; 0.09 mmol; 32%).

Melt

General method D_p was followed using 1,4-benzoquinone (187.1 mg, 1.7 mmol) and dodecylamine (217.2 mg; 1.17 mmol) with a molar ratio of 3:2 at room temperature to provide the title compound (61.1 mg; 0.13 mmol; 22%).

Following the general methods, the title compound (bright orange) was obtained after purification using 99.5:0.5 chloroform:methanol as eluent. m.p. 122-123°C; R_f 0.9 (98/2 $CHCl_3$/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$ at 21°C) δ = 0.88 (t, ^3J= 7.0 Hz, 6H, CH_2-CH_3), 1.16-1.35 (m, 36H, CH_2-CH_2), 1.56 (quintet, ^3J= 7.0 Hz, 4H, NH-CH_2-CH_2), 3.07 (q, ^3J= 6.5 Hz, 4H, NH-CH_2), 5.23 (s, 2H, C-C*H*-C), 6.54 (br t, ^3J= 5.5 Hz 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$ at 21°C) δ = 14.1 (CH_3-CH_2), 22.7, 26.9, 28.2, 29.2, 29.3, 29.4, 29.5, 29.6 (CH_2CH_2), 31.9 (NH-CH_2-CH_2), 42.6 (NH-CH_2-CH_2), 92.6 (*C*H=C-NH), 151.4 (CH=*C*-NH), 178.0 (*C*=O).

2,5-di(octadecylamino)1,4-quinone (C18*p*):

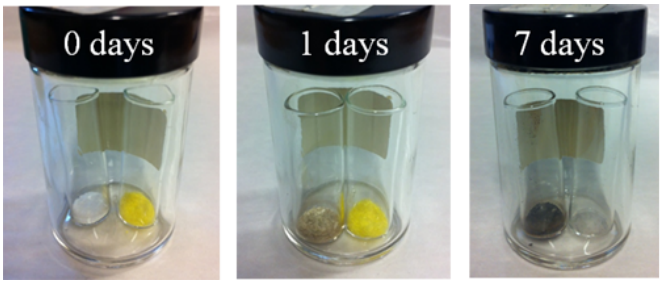

Figure S1. Vapor-mediated synthesis of 2,5-di(octadecylamino)-1,4-quinone, **C18*p***. With time, the quantity of yellow 1,4-benzoquinone decreases and white octadecylamine gradually darkens, which indicates a reaction has occurred

Conventional solvent synthesis

General method A_p was followed using 1,4-benzoquinone (74.8 mg; 0.69 mmol) and octadecylamine (125.5 mg; 0.47 mmol) with a molar ratio of 3:2 to provide the title compound (32.9mg; 0.05 mmol; 22%).

Lysis milling

General method B_p was followed using 1,4-benzoquinone (36.5 mg, 0.34 mmol) and octadecylamine (61.8 mg; 0.23 mmol) with molar ratio of 3:2 to provide the title compound (20.6 mg; 0.03 mmol; 28%).

Ball milling

General method C_p was followed using 1,4-benzoquinone (75.1 mg; 0.69 mmol) and octadecylamine (126.3 mg; 0.47 mmol) to provide the title compound (41.3 mg; 0.06 mmol; 27%).

Melt

General method D_p was followed using 1,4-benzoquinone (153.3 mg, 1.4 mmol) and octadecylamine (256.1 mg; 0.95 mmol) at room temperature to provide the title compound (64.8 mg; 0.10 mmol; 21%).

Following the general methods, the title compound (bright orange) was obtained after purification using 99.5:0.5 chloroform:methanol as eluent. m.p. 117-118°C; R_f 0.93 (98/2 $CHCl_3$/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$ at 21°C) δ 0.88 (t, ^3J= 7.0 Hz, 6H, CH_3), 1.2-1.4 (m, 60H, CH_2-CH_2-CH_2), 1.65 (q, ^3J= 7.3 Hz, 4H, NH-CH_2-CH_2), 3.15 (quartet, ^3J= 6.7 Hz, 4H, NH-CH_2), 5.30 (s, 2H, O-C-C*H*), 6.61 (br t, ^3J= 5.5 Hz, 2H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$ at 21°C) δ = 14.1 (*C*H_3-CH_2), 22.7 (CH_3-*C*H_2), 27.0, 28.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7 (*C*H_2CH_2), 32.0 (NH-CH_2-*C*H_2), 42.6 (NH-*C*H_2-CH_2), 92.7 (*C*H=C-NH), 151.4 (CH=*C*-NH), 178.1 (*C*=O), MS (Triple Quad-ESI): m/z: 643.65 $[M+H]^+$ calcd $[M+H]^+$: 643.61.

3. Powder X-ray Diffraction Patterns

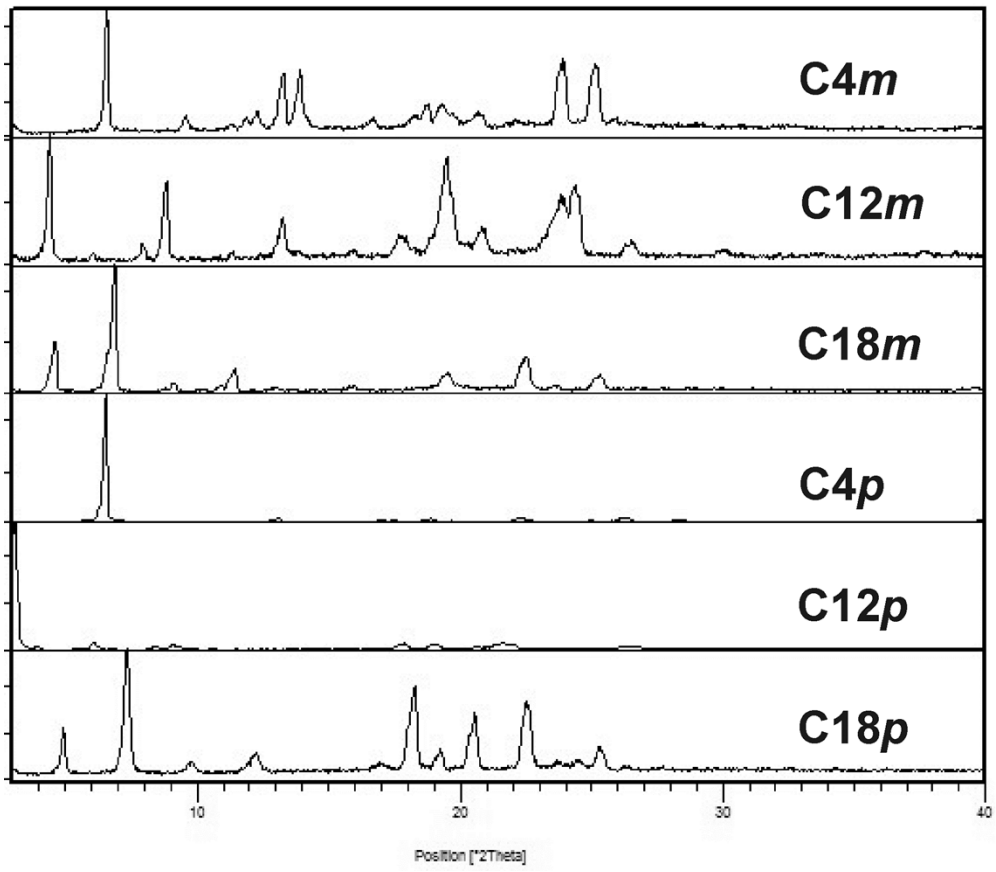

Figure S2. Overlay of powder X-ray diffraction patterns for (top to bottom): **C4*m***, **C12*m***, **C18*m***, **C4*p***, **C12*p*** and **C18*p***. The patterns were collected using Ni-filtered CuK_α radiation.

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