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Enhancement of the Water Solubility of Aromatic Molecules Via the Heck Reaction. A Comparison of Ethano-Ammonium, -Carboxylate and -Phosphonate Functional Groups.

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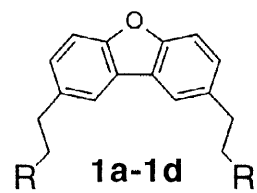
Abstract:

The solubility of aromatic compounds in aqueous solution is difficult to predict due to the lack of systematic solubility data and the inherent difficulties associated with theoretical predictions. Synthetic methodology is introduced for incorporating an ethano-phosphonate solubilizing group into aromatics, which has been used previously to introduce ethano-carboxyl and ethano-amino groups into aromatics. The aqueous solubility of these derivatized aromatics were carefully evaluated at 25°C so that others may use this data to further develop prediction algorithms and make simple predictions regarding solubility.

Systematic studies on small, well-defined β-sheet model systems composed predominantly of α-amino acids and incorporating the folding nucleator 4-(2'-aminoethyl)-6-dibenzofuranpropionic acid, [1-3] have uncovered peptide sequences that are insoluble in aqueous solution. A reliable strategy to enhance the water solubility of a wide range of peptide sequences is desirable and may be achieved by functionalizing the unnatural aromatic nucleating residue with hydrophilic groups. The feasibility of this strategy was tested on the aromatic ring of dibenzofuran. Dibenzofuran, which is insoluble in aqueous solution, was substituted at both the 2 and the 8 positions with either an ethyl-ammonium, -carboxylate, -phosphonate monoester or -phosphonate which allows quantitative comparison of some of the most useful groups for enhancing water solubility (Figure 1) [4-15].

Compound	Absorbtivity ($L\ mol^{-1}\ cm^{-1}$)	Solubility (mol/L)
1a	17,381	1.22
1b	16,720	1.46
1c	15,123	0.55
1d	16,973	0.14



1a: R = NH_3^+ Cl^-
1b: R = CO_2^- Na^+
1c: R = $PO_3CH_3^-$ NH_4^+
1d: R = PO_3H^- NH_4^+

Figure 1 Molar Absorptivity and Solubility of Dibenzofurans 1a, 1b, 1c and 1d in Water at 25°C

The aqueous solubility of organic compounds is a key factor influencing the biological activity of drugs and is an important factor in the biodegradation of organics in the environment. Despite significant accomplishments, it is still difficult to predict the solubility of organics in aqueous solution due in part to the lack of systematic solubility data in the literature and to the inherent difficulties in predicting solubility [4-15]. The aqueous solubility of a compound is largely governed by three factors: (1) entropy of mixing; (2) the differences between the solute water interaction energy and the

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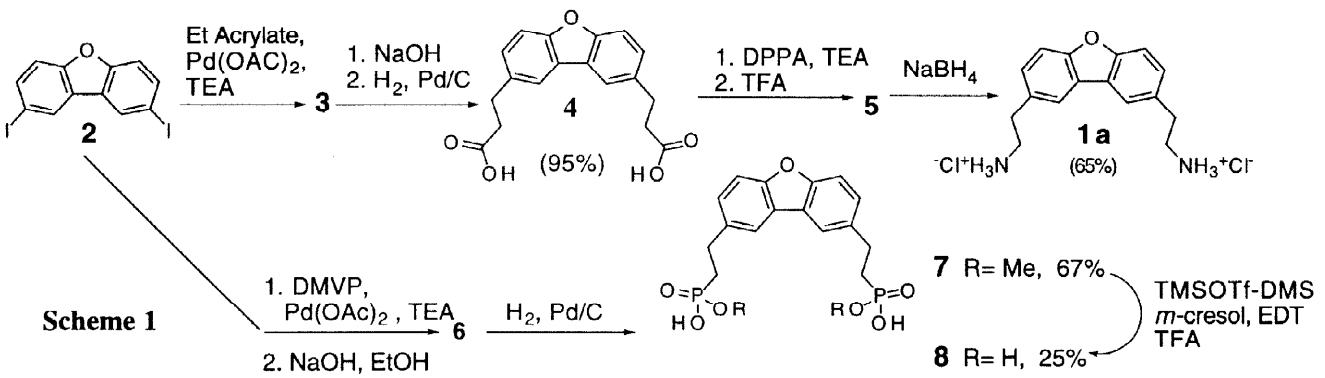
sum of the solute-solute and H_2O-H_2O interaction energies; and (3) the additional solute-solute energetics associated with the lattice energy of crystalline solids. We introduce a new synthetic method for solubilizing organics and provide solubility data that should assist others who need practical information and whose efforts are centered in the important area of solubility predictions.

All of the water soluble dibenzofuran analogs were prepared from 2,8-diiododibenzofuran[16] utilizing Heck reaction conditions. A new Heck-like Pd catalyzed cross-coupling reaction was developed to introduce an ethyl phosphonate ester group onto the aromatic ring. This reaction nicely complements the classical phosphonate ester synthesis carried out by a Michaelis-Arbuzov rearrangement [17-20].



Scheme 1

Results and discussion

The synthesis of the water soluble derivatives **1a**, **1b**, **1c** and **1d** originated with the synthesis of 2,8-diiododibenzofuran **2** derived from the electrophilic aromatic iodination of dibenzofuran.[16] The 2,8-diiododibenzofuran isomer was chosen since functionalization at these positions would not interfere with functionalization at the 4 and 6 positions required for β-sheet nucleation. Furthermore, functionalization at these positions should be predictive of the solublization of aromatics in general. Diiodide **2** was treated with ethyl acrylate employing palladium (II) acetate, which is reduced by triethyl amine to Pd[0] which serves as the catalyst[21-23] affording 2,8-dibenzofuranbis(ethyl-3-propenoate) (**3**) in 99% crude yield (Scheme 1). The ^1H NMR of crude **3** indicated >97% purity with no evidence of remaining starting material **2**. The unsaturated diester **3** was saponified and hydrogenated to afford 2,8-dibenzofuranbis(3-propionic acid) **4** in 95% yield. Isolation of **1b** (Figure 1) was performed by gently heating **4** with a slight excess of NaOH in absolute ethanol until the solids dissolved. The solution was then concentrated under reduced pressure to precipitate **1b**, which was washed with absolute ethanol and dried *in vacuo*.

A tandem Curtius rearrangement of **4** using diphenylphosphoryl azide in toluene[24]yields the bis-isocyanate which was subsequently trapped with trifluoroacetic acid[25] affording 2,8-bis(N-trifluoroaceto-2-aminoethyl)dibenzofuran **5** in 67% yield (Scheme 1). Reduction/deprotection of **5** with sodium borohydride in absolute ethanol, subsequent extraction with ether and back-extraction with dilute HCl afforded 2,8-bis(2-aminoethyl)dibenzofuran dihydrochloride **1a** in 97% yield from **4**.

There are many synthetic strategies that are useful for the synthesis of alkylphosphonates including the Arbuzov reaction,[17-19,26,27] dialkylchlorophosphate trapping of an organolithium species,[28]

Michael addition to dialkylvinylphosphonate[29,30] and radical trapping of white phosphorous followed by oxidation to the phosphonic acid.[31] Since the Heck reaction typically involves the Pd[0] catalyzed reaction of an aryl halide and an acrylate ester,[21,22,32,33] we evaluated the utility of this reaction for the attachment of ethano-phosphonate esters to an aromatic skeleton such as dibenzofuran. A Heck-like reaction between dimethylvinylphosphonate (DMVP) and 2,8-diiododibenzofuran furnished 2,8-dibenzofuranbis(2-vinyl-(*mono*-methyl)phosphonate) **6** in 80% yield after alkaline workup (Scheme 1). Crude product **6** was then subjected to catalytic hydrogenation in water at pH 10 which affords 2,8-dibenzofuranbis(2-ethyl-(*mono*-methyl)phosphonate) **7** in 84% yield. It is known that hydrolysis of both the alkyl ester groups in phosphonate diesters is difficult to achieve under basic conditions, hence it is not surprising that a monoalkyl ester product was formed. We used methodology that was first developed for removal of protecting groups from phosphorylated amino acid residues during solid phase peptide synthesis to hydrolyze the monoethyl ester functional groups[34]. This approach utilizes a strongly acidic medium mixed with strong nucleophiles which remove protecting groups via an acid catalyzed S_N2 mechanism. The removal of the methyl ester groups in Compound **7** was accomplished using a mixture of trimethylsilyl trifluoromethanesulfonate (TMSOTf), dimethyl sulfide (DMS), *m*-cresol, and ethanedithiol (EDT) in trifluroacetic acid (TFA) affording **8** in 25% yield after purification by preparative HPLC. Compound **7** and **8** were dissolved in 0.1 M ammonium carbonate, the samples were frozen and freeze-dried to obtain **1c** and **1d**, respectively (ammonium carbonate is a volatile buffer). This dissolve/freeze-dry procedure was performed three times.

The molar absorptivity of compounds **1a**, **1b**, **1c** and **1d** were determined at 287 nm. All compounds were dried in vacuo over P_2O_5 for 48 h and handled under dry nitrogen. Stock solutions were prepared by dissolving a known mass of the dried compound in a calibrated 10 mL volumetric flask with glass distilled, unbuffered water. Five dilutions of each stock were made affording solutions ranging from 10 μM to 100 μM. The absorbance for each sample was then plotted against its concentration and the molar absorptivity of each dibenzofuran derivative was determined from the slope of the best line through the data points (Figure 1). Samples of **1a**, **1b**, **1c** and **1d** were then incubated at 25°C for 24 h or longer with only enough water to partially solubilize the solids. The saturated solutions were then filtered and serial dilutions were made to 100,000 fold dilution. The absorbance of each diluted sample was then converted into an initial concentration yielding the saturation solubility of each compound (Figure 1).

The pKa's of compound **1d** were determined from a potentiometric titration curve to understand its ionization state in water at pH 6, the final pH of the H_2O used for these solubility studies. It was found that $pKa_1 = 2.30$, whereas, pKa_2 exhibits a broad range of 7.87-9.90. The pKa of compound **1c** was determined to be 2.40, which is well below the pH of the unbuffered water. Thus compound **1d** presents its phosphonates in a monoprotonated state at pH 6.

Conclusions

The ionic dibenzofuran derivatives 2,8-dibenzofuranbis(hydrochloride-2-aminoethyl) **1a**, 2,8-dibenzofuranbis(sodium-3-propionate) **1b**, 2,8-dibenzofuranbis(2-ethyl-(-mono-ammonium,mono-methyl) phosphonate) **1c**, and 2,8-dibenzofuranbis(2-ethyl-(-mono-ammonium) phosphonic acid) **1d** have been prepared to enhance the water solubility of the dibenzofuran skeleton. The bis-carboxylate salt was slightly better at solubilizing dibenzofuran than was the bis ammonium salt, which was better than the bis(mono-methyl) phosphonate salt. The bis-phosphonate salt was the worst of all four derivatives, which was surprising to us. At pH 6 only one of the oxygens of the phosphonate group in **1d** is protonated. It is possible that a hydrogen bonded aggregated species could be forming at saturation solubility making compound **1d** less soluble and possibly explaining the broad apparent pKa_2. A new Heck-like reaction between an aryl iodide and dimethylvinylphosphonate has been introduced to extend the type of water soluble functional groups that can be attached to aryl compounds via the Heck reaction.

Experimental

General Methods and Materials. The dibenzofuran used in these studies was purchased from Lancaster; severely discolored dibenzofuran was purified by sublimation at 1 mm vacuum, 75°C utilizing a water cooled condenser. Dichloromethane and toluene were freshly distilled from calcium hydride prior to use. Anhydrous dimethylformamide (DMF) was purchased from Aldrich. Triethylamine (TEA) was refluxed over ninhydrin, distilled and distilled again from calcium hydride to obtain the pure, anhydrous TEA. Ethyl acrylate (Kodak and Aldrich), Trifluoroacetic acid (TFA, Solvay) and other reagents were used without further purification. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Routine ^{1}H and ^{13}C NMR were obtained on either a Varian XL-200E or unity plus 300; ^{31}P NMR were obtained on a Varian XL-200 or unity plus 300 with a broad band probe. Analytical HPLC was carried out on a Perkin Elmer Bio-410 pump. The column used was an Alltech Versapack C18 (10μ, 4.6 x 250 mm). Detection was accomplished with a Waters Lambda-Max Model 481 variable wavelength UV detector. Solvent A was 95% water, 5% acetonitrile and solvent B was 95% acetonitrile, 5% water; both containing 0.2% TFA.

2,8-dibenzofuranbis(ethyl3-propenoate)(3). To an oven dried 100 mL round bottomed flask cooled under dry nitrogen was added 2,8-diiododibenzofuran **2** (10.5 g, 25 mmol) and palladium acetate (0.112 g, 0.5 mmol). The flask was flushed with dry nitrogen and charged with ethyl acrylate (6.8 mL, 62.5 mmol). An oven dried condenser was attached to the flask and cooled under dry nitrogen after which triethylamine (8.7 mL, 62.5 mmol) and anhydrous N,N-dimethylformamide (30 mL) were added through the condenser. The mixture was heated with stirring in an oil bath at 98°C for 2.5 h. The reaction was cooled to room temperature, diluted in 200 mL of methylene chloride, poured into a 500 mL separatory funnel and washed with 250 mL water (5X). The dichloromethane layer was dried with sodium sulfate, the solids filtered out and the solvent removed under reduced pressure. The resulting gray solid was dried under vacuum to afford 9.07 g (99%) of crude product; >97% pure by NMR. 1H NMR ($CDCL_3$, 200 MHz) δ 8.07 (s, 2H), 7.80 (d, J = 16 Hz, 2H), 7.65 (d, J = 9 Hz, 2H), 7.51

(d, J = 9 Hz, 2H), 6.49 (d, J = 16 Hz, 2H), 4.28 (q, J = 7 Hz, 4H), 1.35 (t, J = 7 Hz, 6H). 13C NMR ($CDCl_3$, 50MHz) δ 167.0, 157.7, 144.2, 129.9, 127.7, 124.3, 120.6, 117.7, 112.3, 60.5, 14.4. Analytical samples were recrystallized from DMF; mp 157-159°C. EI-HRMS m/z for $C_{22}H_{20}O_5$ [M+] Calculated 364.1311, Found 364.1303.

2,8-dibenzofuranbis(3-propionicacid)(4). In a 250 mL round bottomed flask fitted with a reflux condenser, crude 2,8-bis(ethyl 3-propenoate)dibenzofuran **3** (9.1 g, 25 mmol) and NaOH (8.0 g, 0.2 moles) were heated to 85°C in 180 mL of absolute ethanol. After 2.5 h of stirring at reflux, the milky reaction was cooled to room temperature and further cooled in an ice bath. The solids were filtered out and dried under vacuum to afford crude 2,8-dibenzofuran-bis-(sodium 3-propenoate).

The crude product was dissolved in 250 mL of distilled water in a 500 mL parr bottle with sonication. To the solution was added 10% Pd/C (1.0 g) and the bottle connected to a hydrogenation apparatus. The solution was degassed by aspirator and flushed with hydrogen. This degassing/flush procedure was repeated three times and the bottle finally charged with hydrogen to 45 psi. The reaction was allowed to proceed until judged complete by ^1H NMR.

Once the hydrogenation was complete, the catalyst was filtered using a 0.22 μm acetate filter affording an auburn colored liquid which was cooled in an ice bath. Concentrated HCl was added dropwise to the cooled solution with mixing to acidify the solution to pH 1. The precipitated product was filtered out and dried under vacuum to afford 7.14 g (95%) of crude 2,8-dibenzofuranbis(3-propionic acid) **4** as a white powder; mp 209-213°C. Diacid **4** was recrystallized by heating the crude solid in water (1 g of diacid/50 mL) and adding the minimum amount of hot ethanol to dissolve the solid. The solution was hot filtered to remove traces of catalyst; mp 219-221°C. ^1H NMR (DMSO-d6, 200 MHz) δ 12.1 (s, 2H, acid), 7.95 (s, 2H), 7.57 (d, J = 9 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 3.0 (t, J = 7 Hz, 4H), 2.65 (t, J = 7 Hz, 4H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 174.0, 154.7, 136.0, 128.1, 123.8, 120.6, 111.6, 36.0, 30.6. EIMS m/z for $C_{18}H_{16}O_5$ [M+] Calculated 312.0998, Found 312.0994.

2,8-dibenzofuranbis(sodium-3-propionate)(1b). In a 250 mL round bottomed flask was added 2,8-dibenzofuranbis(3-propionic acid) (1.75 g, 5.6 mmol), NaOH (0.48 g, 12 mmol) and absolute ethanol (175 mL). The mixture was gently heated with stirring until all of the solids dissolved. The solution was allowed to cool and the volume reduced under reduced pressure to precipitate the disodium salt **1b**. The solids were rapidly filtered out and washed with 10 mL of cold absolute ethanol after which the solids were dried and stored in vacuo. The mother liquor was concentrated and the solids filtered, washed and dried twice more to afford 1.7 g (85%) of 2,8-dibenzofuranbis(sodium-3-propionate) (**1b**). Analytical HPLC indicated the presence of one homogeneous product which was used in the solubility studies without further purification.

2,8-dibenzofuranbis(N-trifluoroacetyl-2-aminoethyl)(5). To an oven dried 50 mL round bottomed flask, equipped with a reflux condenser and magnetic stirring bar, cooled under dry nitrogen was added 2,8-dibenzofuranbis(3-propionic acid) **4** (3.12 g, 10 mmol), diphenyl phosphoryl azide (4.4 mL, 20.5 mmol), and dry toluene (20 mL). Triethylamine (3.0 mL, 21.5 mmol) was then added to the heterogeneous mixture effecting solubilization within 15 min. The reactants were stirred at room temperature for 1 h and then heated at reflux for 2.5 h. The reaction was cooled to approximately

40°C and trifluoroacetic acid (5 mL, 64.9 mmol) was added. The reaction was then heated at reflux for an additional 18 h.

The reaction was allowed to cool to room temperature slowly, so that the product would crystallize. The solid was filtered out and recrystallized once from toluene affording 2.62 g (69%) of 2,8-bis(N-trifluoroacetyl-2-aminoethyl)dibenzofuran **5**; mp 172-174 °C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.53 (t, 2H), 7.93 (s, 2H), 7.60 (d, J = 9 Hz, 2H), 7.34 (d, J = 9 Hz, 2H), 3.50 (q, J = 7 Hz, 4H), 2.96 (t, J = 7 Hz, 4H). ^{13}C NMR (DMSO-d_6, 50MHz) δ 191.5, 154.5, 133.4, 128.2, 123.5, 120.7, 111.3, 40.9, 33.9. EI-HRMS m/z for $C_{20}H_{16}F_6N_2O_3$ [M+] Calculated 446.1065, Found 446.1080.

2,8-dibenzofuranbis(hydrochloride-2-aminoethyl)(1a). 2,8-bis(N-trifluoroacetyl-2-aminoethyl)dibenzofuran 5 (4.46 g, 10 mmol), sodium borohydride (1.55 g, 40 mmol) and absolute ethanol (40 mL) were added to an oven dried 100 mL round bottomed flask, equipped with a condenser and magnetic stirring bar, and heated at reflux for 2 h under dry nitrogen. The reaction was then allowed to cool to room temperature and acetone (10 mL) was added slowly with stirring to destroy the excess sodium borohydride; the solution was stirred for 15 min after the acetone was added. The solvent was then removed under reduced pressure and the solids dissolved in 30 mL of deionized water. The aqueous solution was saturated with K_2CO_3, and extracted with ether (6 x 30 mL). The ether layer was then extracted with 0.1 M HCl(aq) (2 x 30 mL) and the combined water layers were freeze dried affording 3.19 g (97%) of 2,8-bis(2-aminoethyl)dibenzofuran dihydrochloride **1a**. The product was judged to be pure by C18 RP-HPLC and ^{1}H NMR. The resulting solid was then recrystallized by dissolving the solid in boiling ethanol and adding toluene slowly, ensuring that the solvent continues to boil. When the salt begins to crystallize out, the heat was turned off and the solution was allowed to cool slowly on the hot plate. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.38(s, 6H), 8.05 (s, 2H), 7.65 (d, J= 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H) 3.17 (s, 8H). ^{13}C NMR (DMSO-d6, 50MHz) δ 155.2, 132.7, 128.6, 124.0, 121.3, 112.0, 32.8. EI-HRMS m/z for C16H18N2O [M+] Calculated 254.1419, Found 254.1397. Analytical HPLC indicated the presence of one homogeneous product which was used in the solubility studies without further purification.

2,8-dibenzofuranbis(2-vinyl-(mono-methyl)phosphonate)(6). To an oven dried 50 mL round bottomed flask cooled under dry nitrogen was added **2** (4.20 g, 10 mmol), and palladium (II) acetate (48 mg, 21.4 μmol). The flask was flushed with dry nitrogen and charged with dimethylvinylphosphonate (3.91 mL, 28 mmol, 85% pure) and fitted with an oven dried condenser cooled under dry nitrogen. Triethylamine (3.9 mL, 28 mmol) and DMF (12 mL) were added through the condenser and the materials heated @ 80°C in an oil bath for 12 h. The reaction was then cooled to room temperature and concentrated to 3-5 mL under reduced pressure. The brown, oily residue was transferred to a 125 mL Erlenmeyer flask, dissolved in ethanol (50 mL) and 2 N NaOH (25 mL) was added to the solution. The solution was boiled for 30 min and hot filtered through a Whatman filter to remove any solids. The solution was allowed to cool to room temperature, filtered again, cooled to ice bath temperature and acidified to pH 1 with concentrated HCl. The precipitated product was filtered and dried under vacuum affording 3.28 g (80%) of crude 6; mp 225-226°C. ^{1}H NMR (D_2O, pH~10, 400 MHz) δ 7.52 (s, 2H) 7.35 (d, J = 9 Hz, 2H) 7.13 (d, J = 9 Hz, 2H) 7.20 (t, J = 17 Hz, 2H) 6.28 (t, J = 17 Hz, 2H) 3.48-3.56 (d, J = 11 Hz, 6H). ^{13}C NMR (D_2O, pH~10, 50 MHz) δ 155.9, 144.7, 144.6, 130.6, 130.2, 126.7,

123.1, 118.8, 118.6, 115.0, 111.0, 52.0, 51.9. ^{31}P NMR (D_2O, pH~10) δ 17.6. FAB-HRMS [M+H]+ calculated 409.0606; Found 409.0601.

2,8-dibenzofuranbis(2-ethyl-(mono-methyl)phosphonate)(7). To a 500 mL Parr bottle was added 6 (3.06 g, 7.5 mmol), distilled water (200 mL) and NaOH (1 g). All of the solids dissolved after five min of hand mixing. To the solution was then added Pd/C 10% (1.0 g) and the bottle connected to a hydrogenation apparatus. The solution was degassed via aspirator and flushed with hydrogen. This degassing/flush procedure was repeated three times and the bottle finally charged with hydrogen to 45 psi. Once the conversion was complete as judged by ^{1}H NMR, the catalyst was filtered out using a 0.22 μm acetate membrane. The catalyst was washed with water (2 x 25 mL) and the combined sample and washes cooled to ice bath temperature. The sample was slowly acidified to pH 1 where the crude product **7** precipitated. If an oil was recovered, the flask was scratched until solid product formed . The crude product was crushed in the water and filtered to afford 2.60 g (84%) of **7**. The solids were recrystallized from ethanol and water (see the recrystallization procedure for **4**), mp 179-180°C. ^{1}H NMR (D_2O, pH~10, 400 MHz) δ 7.61 (s, 2H) 7.22-7.25 (m, 4H) 3.59 (d, J = 10 Hz,6H) 2.87-2.93 (m, 4H) 1.94-2.02 (m, 4H). ^{13}C NMR (D_2O, pH~10, 50 MHz) δ 157.1, 139.8, 139.4, 130.0, 126.4, 122.3, 113.8, 54.2, 54.0, 32.2, 31.9,31.8, 29.6. ^{31}P NMR (D_2O, pH ~10) δ 28.5. FAB-HRMS $[M+H]^+$ calculated 413.0919; Found 413.0921.

2,8-dibenzofuranbis(2-ethyl-(mono-ammonium,mono-methyl)phosphonate) (1c). To a 100 mL round bottomed flask was added 2,8-dibenzofuranbis(2-ethyl-(mono-methyl) phosphonate) (**7**) (2.0 g) and .1M ammonium carbonate solution (40 mL). The solids dissolved, the solution was frozen and the water removed by freeze drying. This procedure was repeated three times to afford 2,8-dibenzofuranbis(2-ethyl-(mono-ammonium,mono-methyl) phosphonate) (**1c**) which was stored in vacuo. Analytical HPLC indicated the presence of one homogeneous product which was used in the solubility studies without further purification.

2,8-dibenzofuranbis(2-ethylphosphonicacid)(8). An oven dried 100 mL round bottom flask was charged with 0.219 g of **7** and 20 mL of TFA. To the stirring solution at 0 °C was added TMSOTf (6.5 mL, 33.63 mmol), DMS (4.4 mL, 60 mmol), EDT (1.5 mL), and m-cresol (1.5 mL). The reaction solution was allowed to stir at 0 °C for 30 min and then at 25 °C for 2.5 h. The solvent was then removed under reduced pressure. 15 mL of 1M NaOH was added to the mixture, which was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the layers were separated. The aqueous layer was acidified with HCl to pH 9-10. The crude compound **8** that precipitated was filtered and dried under high vaccum. The crude was purified by C18 RP-HPLC using the gradient 20% solvent B to 75% solvent B over 20 min. The fractions containing the product were freeze dried to give 48 mg (25%) of white powder. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.97 (s, 2H) 7.54 (d, J = 9 Hz, 2H) 7.34 (d, J = 9 Hz, 2H) 2.88-2.96 (m, 2H) 1.85-1.96 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.704, 134.186, 133.952, 124.899, 121.027, 117.468, 108.702, 28.354, 26.571, 26.190. ^{31}P NMR (DMSO-d_6, 121MHz) δ 26.2. FAB-HRMS $[M + H]^+$ calculated 385.0606; found 385.0606.

2,8-dibenzofuranbis(2-ethyl-(mono-ammonium)phosphonicacid)(1d) To a 25 mL round bottom flask was added 30 mg of 8 and 0.1M $(NH_4)_2CO_3$ (10 mL). The dissolved material was freeze dried. This procedure was repeated three times to assure full conversion of **8** to **1d**.

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