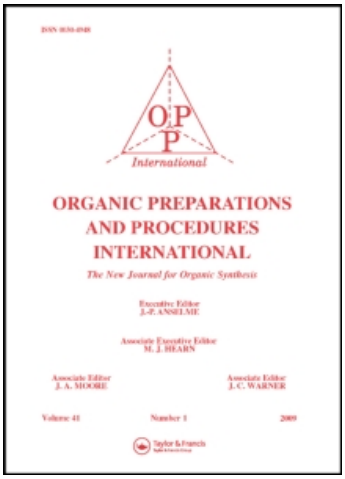

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SYNTHESIS OF TETRAHEDRAL CARBOXAMIDE HYDROGEN BOND ACCEPTORS

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SYNTHESIS OF TETRAHEDRAL CARBOXAMIDE HYDROGEN BOND ACCEPTORS

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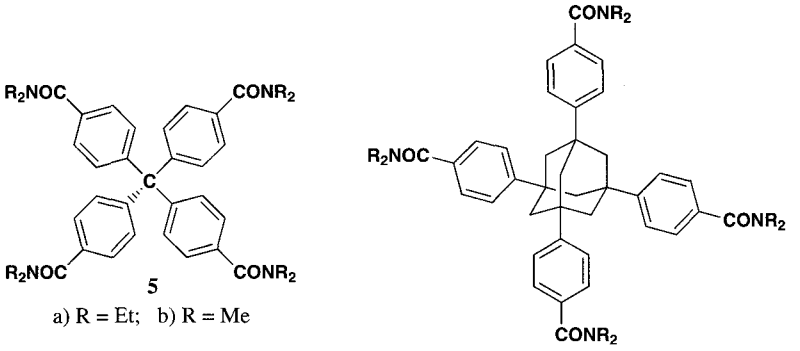
As the field of crystal engineering continues to develop,[1-3] recent advances have shifted the focus of many researchers from the solution to the solid state of molecules. We have found that materials of interest can be manipulated through a process called non-covalent derivatization.[3] An understanding of the non-covalent behavior of molecules may lead to a change in their bulk physical properties.[4-6] Non-covalent forces such as hydrogen bonding, charge transfer, lipophilic interactions and electrostatic interactions may be used to trap the molecule in a crystalline matrix. The manipulation of molecules utilizing the natural processes of molecular recognition and self-assembly, has been demonstrated to be an environmentally benign alternative to traditional covalent synthesis.[7,8] Because of these environmental benefits, crystal engineering and the application of non-covalent derivatization is a growing part of the field of green chemistry.[9,10]

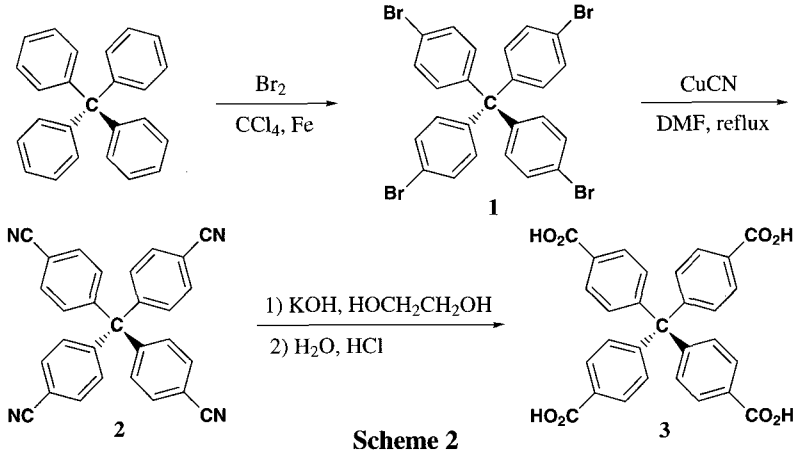
As part of our research efforts, we sought to develop a structure-activity data base so that the implications of crystal packing of co-crystalline matrices on physical properties might be predicted.[11] Our attempts have focused specifically on binary systems whose primary non-covalent structure is based on the phenol-amide hydrogen bond. Previously we reported that *bis*-amides (*bis*-hydrogen bond acceptors) complex with hydroquinone (*bis*-hydrogen bond donors) to form a co-crystalline matrix.[4] This non-covalent derivative exhibits unique properties, independent of the two individual parent components of the co-crystal.[12,13] We have extended this work to include hydrogen bond acceptor components whose functional groups are oriented in trigonal planar[14] and square planar[15] arrays. This report describes the synthesis of hydrogen bond acceptors whose functional groups are oriented in a tetrahedral geometry. There have been reports in the literature of using tetraphenylmethane and tetraphenyladamantane as scaffolding for other synthons containing carboxylic acids and phenols.[16,17] We sought to construct dialkylamide derivatives of these two systems. These tetrahedral amides have similar geometry, but different interatomic distances between hydrogen bond acceptors (the adamantane scaffolding provides an additional 2.4 Å of interatomic distance between amide carbonyls).

The effect of alkyl substitution of the amide nitrogens on structural features of the co-crystalline matrices with hydroquinone has been reported.[18] Consistent features in packing have been observed between methyl and ethyl substitutions. The present study describes the synthesis of dimethyl and diethyl amide derivatives of both tetrahedral systems, namely tetrakis[4-N,N-diethylaminophenyl]methane (**1**), tetrakis[4-N,N-dimethylaminophenyl]-methane (**2**), tetrakis[4-N,N-diethylaminophenyl]adamantane (**3**) and tetrakis[4-N,N-dimethylaminophenyl]adamantane (**4**) (*Scheme 1*).



Scheme 1

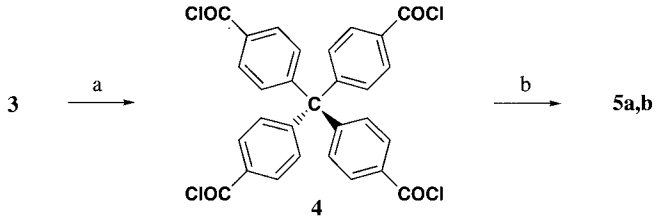
The synthesis of tetraphenylmethane amides **5** and **10** begins with commercially available tetraphenylmethane, which can be converted to the bromide **1** *via* bromination by the method of Hoskins and Robson.[19] Conversion to the nitrile[19] **2**, followed by hydrolysis under basic conditions gave the carboxylic acid intermediate **3**.[20] This reaction gave high yields of the crude acid which could be used in the next step without further purification (*Scheme 2*).



Scheme 2

The conversion of **3** to the desired amides **5a** and **5b** was accomplished *via* a straightforward two-step sequence (*Scheme 3*). The acid **3** was first converted to the acid chloride **4** using oxalyl chloride,[21] followed by treatment of **4** with diethylamine or dimethylamine to

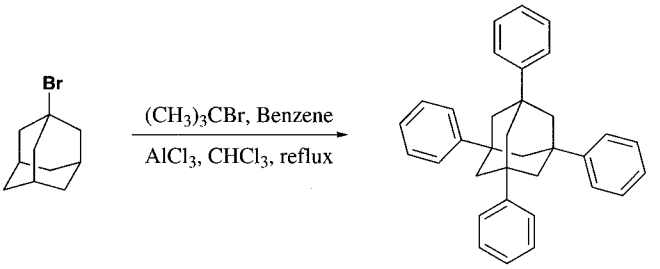
produce the tetraphenylmethane amides **5a** and **5b**.[22]



a) ClCOCOCl, CH_2Cl_2, DMF (cat.); b) Et_2NH (93% yield) or Me_2NH (98% yield), CH_2Cl_2, –15°C

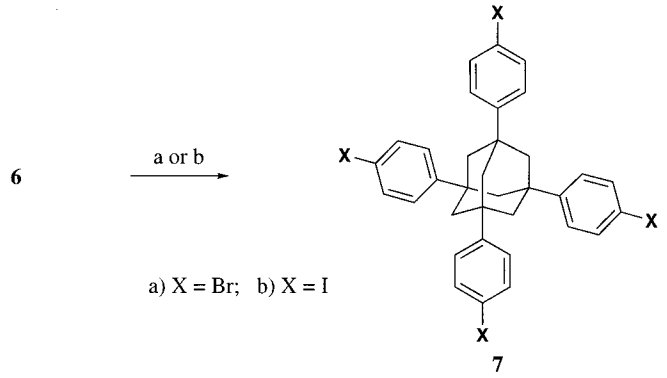
Scheme 3

The tetraphenyladamantane derivatives were somewhat more challenging due to the poor solubility of the parent compound. Tetraphenyladamantane **6** was synthesized by a Friedel-Crafts reaction of benzene with 1-bromoadamantane and *t*-butyl bromide as reported by Newman[23] (*Scheme 4*).



Scheme 4 **6**

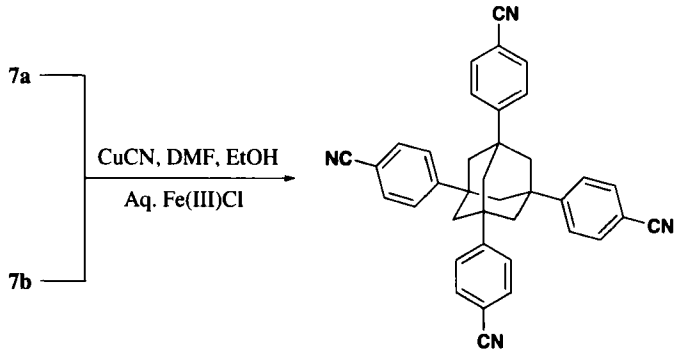
Bromination of **6** was carried our in a manner similar to that used for tetraphenylmethane (*Scheme 6*). We found higher temperatures not only accelerated the bromination but also led to higher yields. Conversion of the bromide derivative **7a** to the nitrile **8** was un-satisfactory; therefore we chose to investigate the reactivity of the iodo derivative **7b**. Compound **7b** was synthesized by the reaction of **6** with iodine and [bis(trifluoroacetoxy)-iodo]benzene (BFIB) in chloroform (*Scheme 5*) to yield tetrakis(4-iodophenyl)adamantane (**7b**).[24]



a) Br_2CHCl_3, Fe, 45-50°C, 94%; b) I_2, $C_6H_5I(OCOCF_3)_2$, $CHCl_3$, 88%

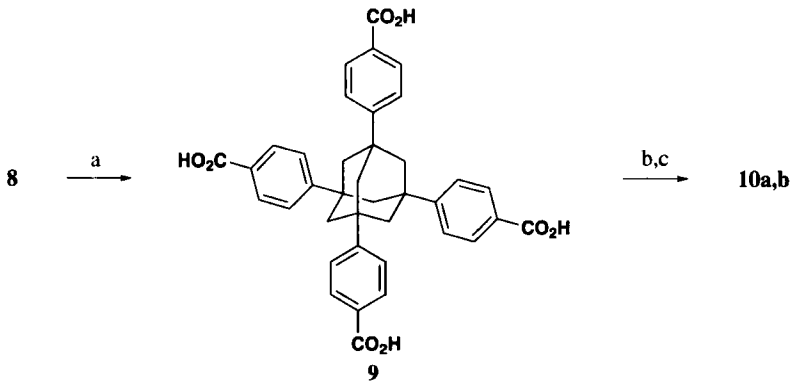
Scheme 5

It was possible to convert both **7a** and **7b** to the nitrile derivative **8** by a procedure similar to that used for tetraphenylmethane **2**.[19, 27] While the conversion of **7a** to the tetrakis-(4-cyanophenyl)adamantane **8** was low, a similar procedure using the iodo derivative **7b** afforded very high yields of the nitrile **8** (*Scheme 6*).



Scheme 6

Conversion of the nitrile **8** to tetrakis[4-(diethylamino)phenyl]adamantane (**10a**) and tetrakis-[4-(dimethylamino)phenyl]adamantane (**10b**) proceeded in a similar fashion to that of the tetraphenylmethane derivatives (*Scheme 7*).



a) KOH, $HOCH_2CH_2OH$, reflux, 99%; b) ClCOCOCl, CH_2Cl_2, DMF (cat.), 0°Cl c) EtNH (3), Me_2NH (4), CH_2Cl_2, –10°C, 96% (3), 94% (4)

Scheme 7

Having these tetrahedral hydrogen bond acceptor building blocks in hand, we plan to construct binary co-crystalline systems in order to compare these geometries to the planar and linear systems previously reported by us.[4, 11, 12]

EXPERIMENTAL SECTION

Proton NMR spectra were recorded on a Bruker AC3000 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS. Melting points were obtained using a

Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by the Microanalysis Laboratory at the University of Massachusetts Amherst. Reagents were obtained commercially and used without further purification.

tetrakis[4-(Diethylamino)phenyl]methane (5a).- Oxalyl chloride (5 mL) was added to tetrakis(4-carboxyphenyl)methane (**3**) (0.8031 g, 1.62 mmol) at 0°C, one drop DMF *via* a syringe was added as a catalyst. The mixture was stirred for 4 h at room temperature. The excess of oxalyl chloride was evaporated under reduced pressure, and diethylamine (5 mL) was added via syringe to the crude acid chloride in methylene chloride (10 mL) at -10°C. The mixture was stirred overnight. After removing the solvent and excess diethylamine, the crude product was dissolved in 60 mL chloroform, washed with 10% HCl and water, dried over Na_2SO_4. The solvent was evaporated and the residue chromatographed on silica gel (EtOAc:$CHCl_3$ 2:1) to give 1.083 g (93%). Recrystallization from benzene gave white crystals, mp 311-312°C. IR (KBr) 2979, 2934, 1622, 1457, 1426, 1378, 1284, 1090, 826, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.280 (d, J = 8.0 Hz), 7.231 (d, J = 8.4 Hz), 3.522 (s, broad, 8 H), 3.282 (s, broad, 8 H), 1.216 (s, broad, 12 H). ^{13}C NMR($CDCl_3$, 75 MHz): δ 171.925 (C=O), 147.876 (C-Cq), 136.225 (C-C=O), 131.942 (CH), 127.099 (CH), 65.7364 (Cq), 44.3858 (N-CH_2), 40.3777 (N-CH_2), 15.3579 (CH_3), 13.9499 (CH_3).

Anal. Calcd for $C_{45}H_{56}O_4N_4$: C, 75.41; H, 7.82; N, 7.82. Found: C, 75.32; H, 7.82; N, 7.64

tetrakis[4-(Dimethylamino)phenyl]methane (5b).- The same procedure as that used for the synthesis of tetrakis[4-(diethylamino)phenyl]methane(**5a**) was followed. The crude product was chromatographed on silica gel (acetone:chloroform 3:1). Recrystallization from methylene chloride and benzene provided white crystals (98%), mp 346-347°C. IR (KBr) 2924, 1628, 1489, 1399, 1265, 1080, 1017, 833 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.317 (d, J = 8.0 Hz, 8 H), 7.266 (d, J = 8.4 Hz, 8 H), 3.088 (s, broad, 12 H), 2.995 (s, broad, 12 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.198 (C=O), 148.119 (C-Cq), 135.462 (C-C=O), 131.852 (CH), 127.768 (CH), 65.8359 (Cq), 40.6862 (CH_3), 36.3949 (CH_3).

Anal. Calcd for $C_{37}H_{40}N_4O_4$: C, 73.51; H, 6.62; N, 9.27. Found: C, 73.36; H, 6.76; N, 9.17

1,3,5,7-tetrakis[4-(Diethylamino)phenyl]adamantane (10a).- Oxalyl chloride (5 mL) was added to 1,3,5,7-tetrakis(4-carboxyphenyl)adamantane (**9**) (0.92 g, 1.5 mmol) in anhydrous methylene chloride (10 mL) at 0°C, a catalytic amount of DMF was added via a syringe. The mixture was stirred for 5 h at room temperature, then the excess of oxalyl chloride and solvent was removed under vacuum. Diethylamine (5 mL) was added *via* addition funnel to the crude acid chloride in absolute methylene chloride (10 mL) at -10°C and the mixture was stirred overnight at room temperature. After evaporation of the solvent and excess of diethylamine, the crude product was dissolved in chloroform (100 mL), washed with aqueous hydrochloric acid (10%) and water, and dried over sodium sulfate. The chloroform was evaporated and the residue was purified by chromatography on silica gel with ethyl acetate-chloroform (2:1). Recrystallization from benzene gave 1.213 g (97%) white crystals, mp > 300°C (dec.). IR (KBr) 2977.9,

2933.6, 1632.2, 1471.9, 1427.3, 1380.2, 1313.2, 1287.7, 1095.5, 841.3, 760.1 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.477 (d, J = 8.0 Hz, 8 H), 7.356 (d, J = 8.0 Hz, 8 H), 3.524 (s, broad, 8 H), 3.261 (s, broad, 8 H), 2.148 (s, 12 H), 1.212 (s, broad, 12 H), 1.110 (s, broad, 12 H). ^{13}CNMR ($CDCl_3$, 75 MHz): δ 171.137 (C=O), 150.047 (C-Cq), 135.508 (C-C=O), 126.654 (CH), 125.049 (CH), 47.076 (CH_2), 43.300 (N-CH_2), 43.118 (N-CH_2), 39.336 (Cq), 13.613 (CH_3), 13.559 (CH_3).

Anal. Calcd for $C_{54}H_{68}N_4O_4$: C, 77.47; H, 8.20; N, 6.69. Found: C, 77.38; H, 8.34; N, 6.63

1,3,5,7-tetrakis-(4-(Dimethylamino)phenyl)adamantane (10b).- The procedure used was similar to the synthesis of **10a**. The crude product was chromatographed on silica gel (acetone-chloroform 4:1). Recrystallization from methylene chloride and benzene provided white crystals (94%), mp >300°C (dec.). IR (KBr): 2927.2, 2852.8, 1630.5, 1491.1, 1447.4, 1393.2, 1266.9, 1083.0, 845.8, 726.6 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.485 (d, J = 8.4 Hz, 8 H), 7.406 (d, J = 8.4 Hz, 8 H), 3.091 (s, broad, 12 H), 2.981 (s, broad, 12 H), 2.149 (s, 12 H). ^{13}CNMR ($CDCl_3$, 75 MHz): δ 171.429 (C=O), 150.394 (C-Cq), 131.478 (C-C=O), 127.369 (CH), 124.959 (CH), 47.0585 (CH_2), 39.7168 (N-CH_3), 39.3829 (Cq), 35.3613 (N-CH_3).

Anal. Calcd for $C_{46}H_{52}N_4O_4$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.55; H, 7.41; N, 7.59

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