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PREPARATION OF $^{13}C_8$ DERIVATIVES OF NAPHTHALENE, OCTACHLORONAPHTHALENE AND TWO HEXACHLORONAPHTHALENES

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SUMMARY

A mild high yield sequence is reported for the synthesis of ($^{13}C_8$) naphthalene from ($^{13}C_6$) benzene and ($^{13}C_2$) succinic acid involving Friedel-Crafts condensation, Wolff-Kishner reduction, polyphosphoric acid cycliacylation, sodium borohydride reduction and palladium dehydrogenation. Perchlorination of ($^{13}C_8$) naphthalene gave a good yield of ($^{13}C_8$) octachloronaphthalene from which the ($^{13}C_8$) hexachloronaphthalenes were obtained by zinc/acetic acid reduction.

Key words: ($^{13}C_8$) naphthalene, ($^{13}C_8$) octachloronaphthalene, ($^{13}C_8$) hexachloronaphthalenes, environmental pollutant.

INTRODUCTION

Polychloronaphthalenes (PCNs) have been reported as environmental contaminants (1,2) and a number of synthetic routes have been investigated to prepare appropriate analytical standards (3,4). However, no ^{13}C labelled PCNs have been available for use as internal analytical standards or for quality assurance purposes. We have, therefore, investigated the synthesis of ^{13}C naphthalene as

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a precursor for the preparation of specific ^{13}C-PCNs. No ^{13}C-labelled naphthalene is available commercially and for most purposes the more highly labelled the compound the more effective it would be. The synthetic sequence outlined in Figure 1 seemed the most likely practical method to prepare ^{13}C labelled naphthalene while the commercial availability of ($^{13}C_6$) benzene and ($^{13}C_2$) succinic acid indicated that naphthalene with eight of ten labelled carbons should be a possibility.

Although this sequence represents a variation of the "classical" naphthalene synthesis the available experimental details were not concerned with minimizing losses by simplifying

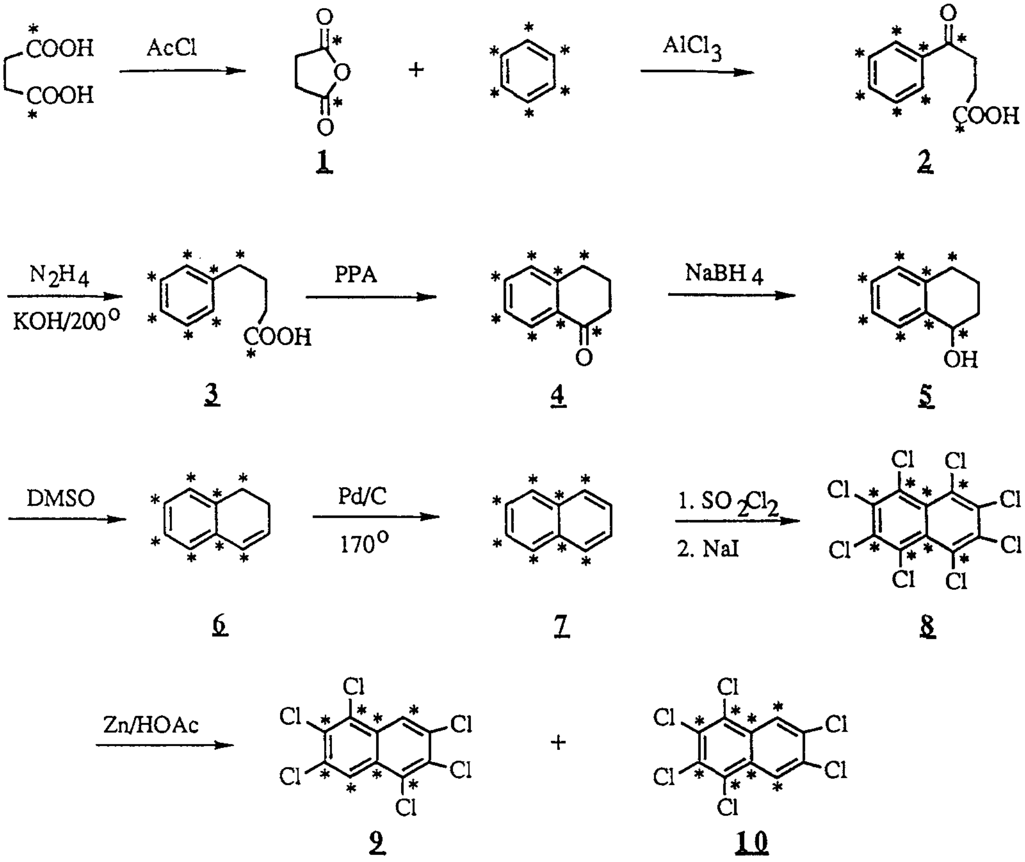

Figure 1: Synthetic Scheme for Naphthalene and the Perchloronaphthalenes

workups. Of particular concern were i) conditions for a high yield of Friedel-Crafts condensation product when stoichiometric amounts of benzene and succinic anhydride were used, ii)a clean, high yield and facile intramolecular cyclization to the tetralone, and iii) the volatility of naphthalene during dehydrogenation and subsequent workup.

The following possible procedures were assembled from the literature. Preparation of succinic anhydride from succinic acid seemed quite straightforward (5). Although most Friedel-Crafts condensations employ excess benzene as a solvent (6), the reaction in tetrachloroethane appeared promising (7). These two procedures were modified to obtain substantially pure materials in good yields. Of the many procedures on reduction of the keto-acid we opted for the Wolff-Kishner (8) conditions because of experimental simplicity. From our previous experience with similar intramolecular acylations (9,10) we expected the polyphosphoric acid (PPA) promoted conditions to be the best compromise between procedural simplicity, high yield and cleanliness of product. The sequence of sodium borohydride ($NaBH_4$) reduction (11) and dehydration (12) was again chosen for mildness (13), experimental simplicity and overall yield (14). The final dehydrogenation step could be accomplished by a variety of reagents (15,16), e.g. dichlorodicyanoquinone (DDQ) (17) but we were hopeful that palladium promoted (Pd/C) dehydrogenation would be a cleaner reaction thus minimizing evaporative work-up procedures with the relatively "volatile" naphthalene (18). Preparation of octachloronaphthalene and the 1,2,3,4,6,7-/1,2,3,5,6,7-hexachloronaphthalene mixture would then employ procedures already well established (3,6,19).

DISCUSSION

Synthetic Procedures

The exact experimental details for each step were perfected during several runs on unlabelled material and in the final simplified format produced a very satisfactory sequence to give better, overall yield and cleanliness of products plus ease of purification where necessary. The use of <u>sym</u> - tetrachloroethane as solvent (7) and extended reaction times permitted the initial Friedel - Crafts acylation of benzene with succinic anhydride to proceed in very good yield despite the restriction, due to cost, of using approximately stoichiometric quantities of the two reactants. Wolff - Kishner conditions for the reduction of keto-acid, <u>2</u>, gave reproducibly good yields. Intramolecular cyclization to the tetralone, <u>4</u>, with (PPA) (9) was experimentally simpler than any other procedures which usually require prior formation of the acid chloride. The "dehydrogenation sequence" from α-tetralone to naphthalene was favoured for several reasons. Both $NaBH_4$ reduction to the tetralol, <u>5</u>, and dimethylsulphoxide (DMSO) dehydration to the dihydronaphthalene, <u>6</u>, were clean, mild and essentially quantitative reactions requiring no "cleanups". In fact acidic workup of the borohydride reaction would effect partial dehydration and might be developed as an alternate approach. The DMSO dehydration was also favoured because of the reduced toxicity relative to hexamethylphosphoric triamide (HMPA), eg. see (20). The dihydronaphthalene, <u>6</u>, is of course now very susceptible to final dehydrogenation to naphthalene and we eventually developed the Pd/C at 170° conditions (21) as a simple, mild, clean and efficient procedure, as compared for example with DDQ treatment (17). The "volatility" of naphthalene becomes a "mixed blessing" at this point. On the one hand, workups involving removal of solvents become more complicated but final purification of product by sublimation becomes very facile. Perchlorination to octachloronaphthalene and subsequent reduction to the hexachloronaphthalenes are well documented procedures (3,6,20).

Characterizations

Traditional spectral methods for characterization were of variable effectiveness. In some instances IR exhibited interesting shifts indicative of the operation of Hooke's Law, eg. in tetralone, 4, the band corresponding to CO stretch peaked at 1642 in the ^{13}C labelled compound versus 1683 in the unlabelled product.

NMR spectra were of limited use due to the intense and extensive, i.e. one-,two- or three-bond effects, for C-C and C-H couplings from the various ^{13}C labelled positions (22). For example, in the ^{13}C labelled 3-benzoylpropanoic acid,2, the ^{1}Hnmr spectrum exhibited a broad, ill-defined set of absorptions in the aromatic region, i.e. 8.5-7.0, while even the peaks due to hydrogen on the unlabelled carbons of the side chain, centered at ~3.3 and 2.8 respectively, exhibited extra splitting due to two-bond (or more) coupling with the neighbouring ^{13}C labelled carbonyl and carboxyl carbons. The ^{13}Cnmr spectrum exhibited complex patterns in the aromatic region (140-126), a "doublet" centred at 199 due to the ^{13}C labelled ketone carbon split by the neighbouring ^{13}C aromatic carbon and a "singlet" at 180 presumably due to the labelled carboxyl carbon which cannot be "affected" by a neighbouring ^{13}C atom. All of these absorptions are of substantial intensity and therefore must represent ^{13}C enriched positions. In contrast the two absorptions representing the side chain carbons (centered at 34 and 28) are of very small intensity and thus indictate no ^{13}C enrichment at these positions. Additionally the absorption at 34 displays a "doublet of doublets" pattern (34.28, 34.00 and 33.42, 33.18) while the absorption at 28 displays a "doublet" pattern (29.11, 28.07) indicative of assignment of these peaks to the carbons α to the ketone and α to the carboxyl respectively with one-bond and three-bond splitting effects from nearby ^{13}C labelled positions. Thus some additional confirmation of the ^{13}C labelled positions can be obtained from this type of analysis on each compound in the series.

MS data for each intermediate clearly indicates the incorporation of eight ^{13}C atoms into the compounds. All labelled compounds displayed identical retention times with the corresponding unlabelled products on various chromatographic methods.

Presumably the same sequence could be employed to generate naphthalene with other labelling patterns depending on which combination of ^{13}C labelled or unlabelled benzene and succinic anhydride was used.

EXPERIMENTAL

GENERAL

IR spectra (ν in cm^{-1}) were obtained on a Perkin Elmer Series 1600 FTIR as thin films on NaCl plates. ^{13}Cnmr spectra (H-decoupled) were acquired from either a Varian XL-200 or a Bruker AMX400 spectrometer and ^{1}Hnmr spectra were obtained from these instruments or a XL-300 instrument. All nmr spectra were taken in $CDCl_3$, unless otherwise indicated, with 1% TMS and all values are recorded in ppm (δ) with reference to TMS. Band shape is indicated by s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet), b(broad). Thin layer chromatography (TLC) was performed on silica gel $60F_{254}$, 0.2 mm thickness on aluminum usually with ethyl acetate/hexane mixtures. Capillary gas chromatography results were obtained with a 30 m x 0.25 mm ID column coated with DB-17 (thickness 0.25 μ). The following standard program was used; inject at 150°, hold 2 min, ramp at 10°/min to 280°, hold for 2 min, then ramp to 300° at 20°/min with final hold after 2 min. Helium was employed as the carrier gas with linear velocity of 37 cm/sec and retention times (R_t) are recorded in minutes. Samples were 10 ppm solutions in hplc grade dichloromethane or hexane. Various instruments were employed: Varian Vista 6000 with FID, Varian 3600 with ECD and a Varian Saturn II GC/MS system, i.e. a series 3400 GC with Ion Trap Detector. Melting points were obtained on a Buchi SMP-20 melting range apparatus and are recorded in degrees Celsius as are all temperatures. Mass spectra were obtained on a VG707E instrument at 70eV under Electron Impact (EI) mode and the significant fragments reported as m/z values (relative intensity). High Resolution mass spectral values (HRMS) were obtained on the molecular ion. The drying agent used in all cases was anhydrous $MgSO_4$. All solvents were distilled in glass. Most reagents were obtained from Aldrich Chemical Co. and were used as received. The following ^{13}C-labelled compounds (99 Atom %) were obtained from Merck Isotopes Ltd.- ($^{13}C_6$)Benzene and (1,4-$^{13}C_2$) Succinic acid. For comparison purposes, analogous spectral data, etc. are provided for the corresponding unlabelled compounds.

($^{13}C_2$) Succinic Anhydride, 1: The ($^{13}C_2$) anhydride was prepared according to the method of Fieser and Martin (5) using $^{13}C_2$ - labelled (50 mmols) to give 91% yield; m.p 118-119° (unlabelled 118-119°). N.B. IR for succinic acid: labelled, 1655; unlabelled, 1693.

($^{13}C_8$) 3-Benzoylpropanoic acid, 2: This acid was prepared as described in (7) using ($^{13}C_2$) Succinic anhydride,1 (4.46g, 45 mmol) and ($^{13}C_6$) benzene (4.00g, 51 mmol) in 1,1,2,2-tetrachloroethane (50 mL) and freshly, powdered $AlCl_3$ (15g) added with stirring in 30 min period at 0°. The resulting dark coloured mixture was then stirred at RT under exclusion of moisture for 5 days before treating with ice (50 g) and conc. HCl. After separation of the organic layer the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) the combined organic extracts were washed with 5% aqueous HCl (1 x 50 mL) followed by water wash (1 x 50 mL) and then extracted with 5%

aqueous NaOH (3 x 75 mL). The basic extracts were washed with CH_2Cl_2 (2 x 30 mL) prior to reacidification to precipitate the acid. This aqueous suspension was extracted with CH_2Cl_2 (3 x 50 mL), the organic extracts were dried over anhydrous $MgSO_4$ and stripped of solvent to produce a white, solid residue, (6.21 g, 78%) of sufficient purity to continue. Treatment with charcoal and crystallization from hexane gave white crystals for spectral characterization. MP: 118.5-119.0°; IR:1643,1549,751; ^{1}Hnmr:11.6(bs,1),8.5-7.0(m,5), 3.3(m,2),2.8(m,2); ^{13}Cnmr:199("d"),180("s"),140-126(m),34 and 28(m, both very small); MS:186(5),112(100),83(44); HRMS:For ($^{13}C_8$) $C_{10}H_{10}O_3$: Calc. 186.08988; Found 186.08921.

Unlabelled 3-benzoyl-propanoic acid: MP:117-119°;IR:1682,1594,764;^{1}Hnmr:11.7(bs,1),8.0(m,2),7.8-7.4(m,3),3.3(t,2),2.8(t,2);^{13}Cnmr:198.1,179.4,136.5,133.5,128.8, 128.2,33.3,28.2;MS:178(5),105(100),77(43).

<u>($^{13}C_8$) 4-Phenylbutanoic acid, 3</u>: The keto-acid,<u>2</u> (3.00 g, 16.1 mmol) was dissolved in diethylene glycol (100 mL) and hydrazine hydrate (64% aqueous, 30 mL) was added. After stirring at RT for 30 min, potassium hydroxide (15 g) was added and the mixture brought to reflux (~120°) for 1.5 hr. Low boiling material was slowly removed until the distillate temperature reached 215° and then the reaction was allowed to reflux for a further 3 hr. After cooling the reaction mixture was poured onto ice (500 g) and this basic aqueous solution (~700 mL) was carefully treated with HCl to pH 2 while a white precipitate formed. The mixture was extracted with diethylether (4 x 75 mL) and the combined organic phases were backwashed with saturated aqueous NaCl (2 x 100 mL). After drying, treating with decolourizing charcoal and stripping solvent a white solid residue (3.0 g) was obtained. This material was of

sufficient purity, by TLC, to continue however it could be crystallized from hexane, (2.77g, 99%). MP: 51.5-52.0°; IR:1650, 785, 685; ^{1}Hnmr:11.5(bs,1),7.6(m,3),6.8(m,2),3.0(m,2), 2.4(m,2), 1.9(m,2);^{13}Cnmr: 180("d"), 143-139(m), 131-123(m), 35("d"), 33 and 26("d", both very small); MS: 172(21), 112(36), 111(100), 98(63); HRMS: For $(^{13}C_8)C_{10}H_{12}O_2$; Calc. 172.11064, Found 172.10926. Unlabelled 4-phenylbutanoic acid: MP: 51-52°;IR:1690,749,700; ^{1}Hnmr:11.5(bs,1),7.4-7.1(m,5),2.6(t,2),2.3(t,2),1.9(q,2); ^{13}Cnmr: 180.9, 141.8, 129.1, 129.0, 126.6, 35.5, 33.9, 26.7; MS:164(22), 105(38),104(100),91(66).

$(^{13}C_8)$ α-Tetralone, 4: Polyphosphoric acid (25 g) in a 125 mL Erlenmeyer flask equipped with magnetic stirrer was heated to 60° so that it was fluid enough to be easily stirred. The phenylbutanoic acid,3 (5.6 g, 32.6 mmol) was added portionwise over 10 min and the dark-coloured reaction mixture was stirred for 2 hr at 100°. The reaction mixture was now treated carefully with cooling and stirring with ice and water so that a volume of 400 mL was ultimately attained. This aqueous mixture was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic layers were backwashed with 5% aqueous NaOH (2 x 50 mL) and water (1 x 50 mL). After drying and carefully removing solvent there remained a yellowish liquid (4.45 g, 89%). This material was deemed sufficiently pure, by TLC, to proceed to the next step but could be further purified by flash chromatography on silica gel with EtOAc:Hexane (1:9) to yield a colourless oil, (4.01 g, 80%). IR:2945,1642,1546,756,717; ^{1}Hnmr: 8.5-6.7(m,4), 3.2(m,2), 2.6(m,2), 2.1(m,2); ^{13}Cnmr: 198("d"), 142-147(m), 136-124(m), 38("d"), 30("d"), 39 and 23("d", both very small); MS: 154(68), 126(100), 97(81); HRMS:For $(^{13}C_8)C_{10}H_{10}O$; Calc. 154.10008, Found. 154.09977. Unlabelled α-tetralone: IR: 2944,1683, 1602,764,735; ^{1}Hnmr: 8.1(m,1), 7.4(m,2), 7.2(m,1), 2.9(t,2), 2.6(t,2), 2.2(q,2); ^{13}Cnmr: 197.6, 144.4, 133.2, 132.5, 128.7, 126.9, 126.4, 39.0, 29.5, 23.2; MS: 146(71), 118(100), 90(58).

($^{13}C_8$) 1,2,3,4-Tetrahydro-1-naphthol, 5: To a solution of ($^{13}C_8$) α-tetralone,4 (3.60 g, 23.4 mmol), in ethanol (absolute, 40 mL) was added $NaBH_4$ (1.2 g, 31.6 mmol). The resulting solution was allowed to stand at RT for 3 hr then diluted with H_2O (200 mL). This solution was extracted with CH_2Cl_2 (4 x 75 mL) and the combined organic layers backwashed with H_2O (3 x 75 mL). After drying and carefully removing solvent, a yellow-coloured viscous oil (3.51 g, 97%) was obtained. This material, which solidified on standing, was judged to be sufficiently pure to continue however crystallization could be effected from hexane.MP: 32-34°;IR:3355,1457,1426,759,729;^{1}Hnmr:7.86.3(m,4),5.0-4.6(m,1),3.0-2.4(m,3),2.2-1.8(m,4);^{13}Cnmr:141-134(m),132-124(m),68("d"),29("d"),32 and 19("d", both very small); MS:156(33),155(37),138(88),137(38),127(100),112(32),98(54);HRMS:For($^{13}C_8$)$C_{10}H_{12}O$;Calc.156.11574,Found.156.11838.Unlabelled α-tetralol:MP:33-34°;IR:3340,1490,1454,774,739;^{1}Hnmr:7.4(m,1),7.5-7.1(m,3),4.8("t",1),2.8(m,3),2.1-1.8(m,4);^{13}Cnmr:139.0,137.4,129.2,128.9,127.8,126.4,68.3,32.4,29.5,19.0;MS:148(33),147(32),130(100),129(49),120(84),91(64).

($^{13}C_8$)1,2-Dihydronaphthalene, 6: The α-tetralol,5,(1.50 g, 10.0 mmol) in anhydrous DMSO (100 mL) was refluxed for 1 hr. After cooling and diluting with H_2O (600 mL) the solution was extracted with hexanes (4 x 75 mL) and the combined organic extracts backwashed with H_2O (3 x 100 mL). After drying, treating with decolourizing charcoal and carefully removing solvent there was obtained a colourless oil (1.21 g, 91%) of sufficient purity (TLC) to continue.IR:2930,1486,1452,782,745;^{1}Hnmr: 7.8-6.0(m),3.3-2.4(m); ^{13}Cnmr:139-131(m),131-122(m),27("d"),23("d",very small); Unlabelled 1,2-dihydronaphthalene:IR:2930,1453,782,745;^{13}Cnmr:135.6,134.3,128.7, 127.9,127.6,127.0,126.6,126.0,27.6,23.3;MS:130(100,129(89),128(81),115(54).

<u>($^{13}C_8$)-Naphthalene, 7:</u> The dihydronaphthalene,<u>6</u> (0.65 g, 5mmol) was added to 10% Pd/C (0.1 g) and this mixture heated at 170° for 1 hr. The reaction vessel was equipped with a reflux condenser to prevent any loss of naphthalene. The cooled mixture was treated with diethylether, the catalyst filtered off and washed with additional ether. Careful removal of the solvent produced a brown-coloured semi-solid residue (0.55 g) which was judged of sufficient purity (GC) to continue with chlorination. Material could be purified by sublimation for spectral characterization. MP:81-81.5°; IR:3037,2910,774,461; ^{1}Hnmr: 8.5-7.0(m);^{13}Cnmr:136-131(m), 130-124(m); MS:136(100);HRMS:For ($^{13}C_8$)$C_{10}H_8$; Calc. 136.08952, Found 136.08660. Unlabelled naphthalene: MP:80-82°;IR:3045,2910,780,480; ^{1}Hnmr:7.9-7.8(dd,1),7.6-7.5(dd,1);^{13}Cnmr:134.0,128.4,126.4;MS:128(100).

<u>($^{13}C_8$)-Octachloronaphthalene, 8</u>: As previously described (3,19) the crude napathalene, <u>7</u>, (1.30 g, 10 mmol, see above) and S_2Cl_2 (0.5 mL) in fresh SO_2Cl_2(50 mL) was slowly added to a refluxing solution of anhydrous $AlCl_3$ (0.5 g) in SO_2Cl_2 (150 mL). Over 1 hr the volume was reduced to 50 mL by slowly distilling SO_2Cl_2 then the reaction was continued at reflux for a further 5 hr. The remaining SO_2Cl_2 was removed and the residue carefully treated with H_2O(100 mL) followed by gradual addition of solid $NaHCO_3$ until no more gas evolved. This mixture was heated at 80° and stirred for 1 hr then cooled, acidified with HCl and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were back-washed with H_2O (2x30 mL), dried and the solvent removed to produce a yellow-brown solid (4.0 g, 84%) with decomposition

temperature of 205°. This was presumably the decachlorodihydronaphthalene intermediate (3,19).

To a solution of this intermediate (1.0 g) in hot acetone (200 mL) was added sodium iodide (1.0 g). After 3 hr reflux the reaction mixture was cooled to RT, diluted with H_2O(200 mL) and the yellowish precipitate filtered and dried (0.80 g, 94% from napthalene). This material contained 85% octachloronaphthalene as judged by GC/MS. A sample of this material was used directly for reduction to the hexachloronaphthalenes. Alternately material could be purified by crystallization from $CHCl_3$ or prep (RP)-HPLC in MeOH. MP:196-197°;^{1}Hnmr: no peaks;^{13}Cnmr: 137-134(m), 132-129(m); MS: 416(25), 414(67), 412 (100), 410 (90), 408(35), 342 (50), 340 (63), 338 (31), 270 (31), 268 (23); HRMS: For ($^{13}C_8$) $C_{10}Cl_8$: Calc. 407.7771 ; Found, 407.77581. Unlabelled octachloro-naphthalene: MP: 197°; ^{1}Hnmr: no peaks; ^{13}Cnmr: 135.3, 129.7, 129.0; MS: 408(39), 406(93), 404(100), 402(54), 400(53), 334(53), 332(67), 330(34), 262(27), 266(22), 166(24).

($^{13}C_8$)1,2,3,5,6,7-/1,2,3,4,6,7-Hexachloronaphthalenes,9+10: Using conditions developed previously (3) the crude octachloronaphthalene,8, (100 mg, 0.25 mmol) was treated with Zn dust (0.13 g) in refluxing glacial acetic acid (40 mL) for 16 hr. The metal was filtered off and, after cooling, the filtrate was diluted with H_2O(400 mL) and the precipitated solid was collected and dried (90 mg, 84%). GC analysis indicated predominantly (90%) a single peak. Recrystallization (2x) from diethylether produced a material showing only 1 peak on GC. MP: 178-180°; ^{1}Hnmr: 8.8 -7.9 (m); ^{13}Cnmr: 137-123(m); MS: 346(34), 344(80), 342(100), 340(51), 272(37), 270(28); HRMS: For ($^{13}C_8$) $C_{10}H_2Cl_6$: Calc. 339.8560; Found, 339.85630. Unlabelled hexachloronaphthalene: MP: 178-181°; ^{1}Hnmr: 8.39, 8.32; ^{13}Cnmr: 134.1, 133.4, 132.1, 131.5, 131.0, 129.2, 129.05, 129.04, 126.7

(strong), 124.6 (strong); MS: 338(35), 336(81), 334(100), 332(53), 264(36), 262(28).

It has been shown by us and others that this material is in fact a mixture of the two indicated isomers. Certain specific LC conditions can achieve partial resolution (3,6).

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