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Preparation and Reactions of 5,6-Bis(bromomethyl)pyrazine-2,3-dicarbonitrile with *S*, *N* and *O* Nucleophiles. Synthesis of Octa(propoxymethyl) Azaphthalocyaninato Magnesium

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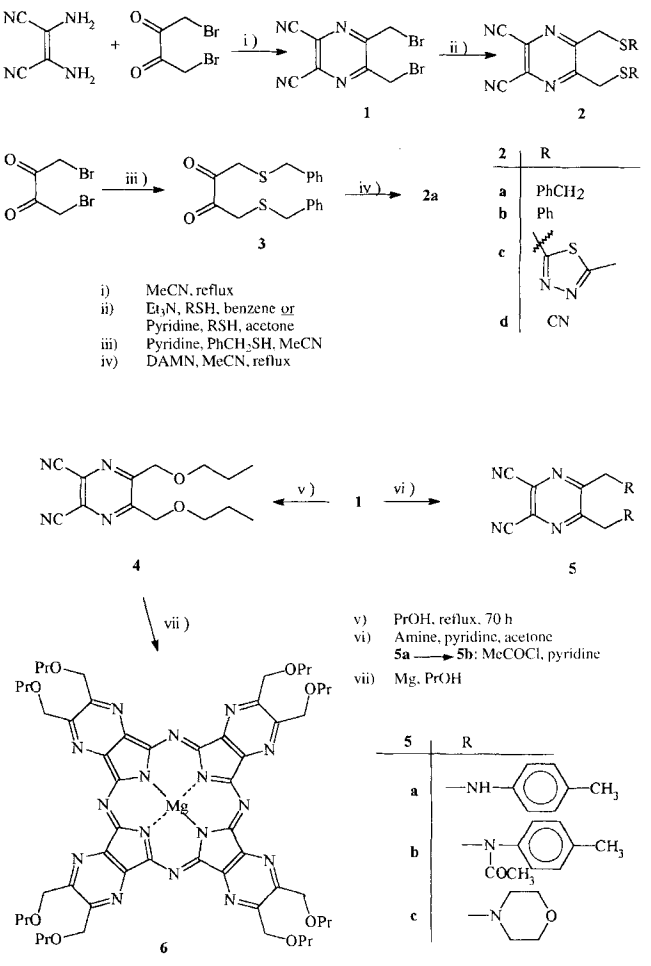
Pyrazine-2,3-dicarbonitriles may be used as precursors for aza analogs of phthalocyanines (AzaPc's). Presently AzaPc's are receiving considerable attention, mainly due to their increased solubility compared to the parent phthalocyanines. Enhanced solubility is caused by the eight additional nitrogens in the macrocycle and may be further increased by the introduction of substituents on the pyrazine ring. For instance, water soluble AzaPc's have been prepared for use in photodynamic therapy [1], new azatriphenylene macrocycles have been reported [2] as potential mesomorphic materials, and some *S*-substituted octasulfanyl AzaPc's have been prepared in our laboratories [3].

The aim of the present work was first to prepare derivatives of **1** with sulfur, nitrogen or oxygen containing side chains, and then to synthesize AzaPc's by cyclotetramerisation of these pyrazine dicarbonitriles. Such compounds might be of potential interest as advanced materials, for instance as low dimensional organic conductors [4], or as activators in photo-dynamic cancer therapy [5].

5,6-Bis(bromomethyl)pyrazine-2,3-dicarbonitrile **1** is obtained in excellent yield from the commercially available diaminomaleonitrile and 1,4-dibromobutane-2,3-dione. The inexpensive diaminomaleonitrile is a well known source for vicinal, unsaturated dinitriles, which have been used for cyclotetramerisations [1–3, 6–7].

Compound **1,** however, is very unstable in the presence of any base or nucleophile. For instance, addition of pyridine to **1** gave immediately a red solution, which turned dark brown in a matter of minutes. We ascribe the base sensitivity of **1** to its „benzylic" methylene hydrogens, which seem even more labile than ordinary benzylic hydrogens. The reactivity of **1** is easily explained by the electron withdrawing effects of the pyrazine ring and the attached cyano groups. Consequently, compound



1 is difficult to handle, and its use as a synthon for AzaPc's is thereby limited.

The reaction of **1** with benzyl mercaptan in the presence of an equimolar amount of pyridine gave a salt which could not be converted to **2a** by treatment with a stronger base. However, when triethylammonium benzylthiolate was prepared, treated with benzene to remove traces of excess triethylamine and then reacted with **1**, compound **2a** was obtained in 75% yield. The reaction of 1,4-bis(benzylsulfanyl)butane-2,3-dione (**3**) and diaminomaleonitrile also gave **2a** in fair yield (61%). Compounds **2b** and **2c** were obtained from **1** and pyridinium thiolates, and **2d** from **1** and potassium thiocyanate.

Reactions of compounds **2a–b** with magnesium propoxide in propanol and dioxane gave decomposition products which seemed to be partly polymeric. During these reactions, the odor of the corresponding thiols was obvious, indicating decomposition of the sulfanyl side chains. At best, an impure MgAzaPc was obtained from **2b** (ε = 30 400 at 650 nm).

Compound **1** is extremely sensitive to base and consequently, the introduction of alkoxide side chains was achieved by prolonged reflux in the corresponding alcohol. Although several alcohols were tested, 1-propanol gave the cleanest product. Even this reaction gave several by-products, which were removed by chromatography, and **4** was obtained in moderate yield (53%). 1-Propanol was used as solvent for the cyclotetramerisation of **4**, so that side chain exchange would be of no consequence. This cyclotetramerisation of **4** with magnesium propoxide in propanol gave a dark blue powder which had the expected chromophore of AzaPc **6**, but with somewhat low extinction coefficient, ε = 38 000 at 636 nm. Chromatography on silica with acetone increased the purity of the product, and one fraction was obtained with ε = 62 500 at 636 nm. However, the rest of the product seemed to undergo some decomposition on the silica column.

Various nitrogen nucleophiles were treated with **1**, but extensive decomposition was observed in most instances. However, a reaction of **1** with *p*-toluidine and pyridine gave the bis(*p*-tolylaminomethyl)pyrazine **5a** in excellent yield (98%). Protection of the labile amine hydrogens of **5a** was required before cyclotetramerisation to AzaPc, but acetylation of **5a** gave the acetylamino compound **5b** in merely 10% yield.

The reaction of **1**, morpholine and pyridine gave the dimorpholino compound **5c** in 37% yield. Attempts to cyclize **5c**, using magnesium propoxide, propanol and dioxane as a cosolvent gave invariably brown solids which had no trace of an AzaPc chromophore.

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Experimental

Mass spectra were obtained on an AEI MS-902 spectrometer at 70 eV electron energy. IR spectra were obtained on a Nicolet 20-SXC FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 NMR spectrometer at 399.65 MHz and at 100.40 MHz, respectively, and with tetramethylsilane (TMS) as internal standard. UV–VIS spectra were obtained on a Perkin Elmer 522 UV–VIS spectrophotometer. Melting points were obtained on a Büchi 530 melting point apparatus and are uncorrected. Merck Kieselgel 60F 254 was used for TLC and Merck silica 63–200 µm was used for column chromatography. Diaminomaleonitrile and 2-mercapto-5-methyl-1,3,4-thiadiazole were obtained from Janssen, and 1,4-dibromo-butane-2,3-dione was obtained from Aldrich. Dioxane was purified by passing through a short column of activated basic alumina S, then stored over molecular sieves, 3 Å, and 1-propanol was dried over potassium carbonate, distilled and stored over molecular sieves, 3 Å.

5,6-Bis(bromomethyl)pyrazine-2,3-dicarbonitrile (**1**)

A solution of 1,4-dibromo-butane-2,3-dione (6.2 g, 25.4 mmol) in acetonitrile (50 ml) was added to a solution of diaminomaleonitrile (2.75 g, 25.4 mmol) in acetonitrile (50 ml). The solution was heated at 70 °C for 1 h, the solvent was removed under reduced pressure and the solid residue was chromatographed on silica with dichloromethane. Yield 7.7 g (96%), *m.p.* 106–108 °C. – MS *m/z* (% rel. int.): 318 (3.5), 316 (7.5, M), 314 (3.5), 238 (10.5), 237 (99.4), 236 (15.9), 235 (100). Found 315.8779, calcd. for $C_8H_4{}^{79}Br^{81}BrN_4$ 315.8782. – IR (KBr) : 3032 (CH stretch), 2975 (CH stretch), 2245 (w, CN), (1534, 1445, 1382 (s), C=C or C=N stretch) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ 4.75 (4H, s). – ^{13}C NMR ($CDCl_3$): δ 27.03 (CH_2), 112.25 (CN), 131.89 (C-2, C-3), 155.37 (C-5, C-6).

5,6-Bis(benzylsulfanylmethyl)pyrazine-2,3-dicarbonitrile (**2a**)

Method A. Triethylamine (2.0 g, 20 mmol) was added to a solution of benzylmercaptan (2.48 g, 20 mmol) in benzene (10 ml). The solvent was removed under reduced pressure, and the liquid residue was redissolved in benzene (10 ml). A solution of **1** (3.2 g, 10 mmol) in benzene (30 ml) was added, and the solution was stirred at ambient temperature for 1h. The reaction mixture was diluted with benzene (20 ml) and extracted with water (2×15 ml). The benzene solution was dried, evaporated to dryness, and hexane was added to the solid residue which was filtered off. Yield of **2a**, 3.0 g (75%), *m.p.* 104–105 °C. No change of *m.p.* was observed upon recrystallisation from benzene. – MS *m/z* (% rel. int.): 404 (1.0), 403 (2.3), 402 (M, 8.1), 311 (3.8), 123 (13.8), 91 (100). Found 402.0967, calc. for $C_{22}H_{18}N_4S_2$ 402.0973. – IR (KBr): (3050 (w), 2990 (w), 2911 (w), CH stretch), 2244 (w, CN), (1529, 1491, 1449, 1374, C=C or C=N stretch) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ 3.69 (4H, s), 3.88 (4H, s), 7.25 (10 H, m). – ^{13}C NMR ($CDCl_3$): δ 34.07, 36.54, 112.79 (CN), 127.41, 128.65, 128.83, 129.89, 136.77, 157.04.

1,4-Bis(benzylsulfanyl)butane-2,3-dione (**3**)

Method B. i) Pyridine (1.58 g, 20 mmol) was added dropwise during 10 min. to a solution of 1,4-dibromobutane-2,3-dione (2.44 g, 10 mmol) and benzylmercaptan (2.5 g, 20 mmol) in acetonitrile (20 ml). The reaction mixture was stirred at ambient temperature for 45 min, and the suspension was diluted with diethyl ether (50 ml). The yellow precipitate was filtered off, washed with water (20 ml) and finally with diethyl ether. Yield of **3**, 2.3 g (70%), *m.p.* 118–120 °C. – MS *m/z* (% rel. int.): 332 (0.4), 331 (0.7), 330 (3.3, M), 239 (8.6), 213 (11.1), 208 (11.3), 190 (8.4), 91 (100). Found 330.0756, calcd. for $C_{18}H_{18}O_2S_2$ 330.0748. – IR (KBr): (3063, 3032, 3002, 2939,

2914, CH stretch), 1696 (vs, C=O), (1493, 1454, 1398, C=C stretch) cm^{-1}. – ^1H NMR ($CDCl_3$): δ 3.46 (4H, s), 3.67 (4H, s), 7.31 (10 H, m). – ^{13}C NMR ($CDCl_3$): δ 32.63, 35.90, 127.35, 128.54, 129.30, 136.54, 189.79 (C=O).

ii) Compound (**2a**)
A mixture of diaminomaleonitrile (0.22 g, 2 mmol) and **3** (0.66 g, 2 mmol) in acetonitrile (20 ml) was heated under reflux for 20 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica with dichloromethane. Yield 0.50 g (61%), *m.p.* 99–101 °C. This product was spectroscopically identical to the product obtained by Method A.

Compounds (2b–2c) (General Procedure)

The thiol (6.1 mmol) was added in one portion to a well stirred solution of compound **1** (0.95 g, 3 mmol) in acetone (40 ml). Pyridine was added dropwise to this solution, stirring was continued for 1.5 h at ambient temperature, and the solvent was removed under reduced pressure. Water (10 ml) was added to the solid residue, which was filtered, washed with water and diethyl ether.

5,6-Bis(phenylsulfanylmethyl)pyrazine-2,3-dicarbonitrile (**2b**)

1.0 g (89%), *m.p.* 137–139 °C, *m.p.* 140–141 °C (methanol). MS *m/z* (% rel. int.): 376 (5.8), 375 (13.3), 374 (50.0 M), 266 (7.1), 265 (27.0), 264 (50.1), 231 (100). Found 374.0657, calcd. for $C_{20}H_{14}N_4S_2$ 374.0660. – IR (KBr) : (3044, 2929, 2894, CH stretch), 2239 (w, CN), (1581, 1525, 1482, 1439, C=C or C=N stretch) cm^{-1}. – ^1H NMR ($CDCl_3$): δ 4.33 (4 H, s), 7.28 (10 H, m). – ^{13}C NMR ($CDCl_3$): δ 38.14 (CH_2), 112.59 (CN), 128.57, 129.38, 130.13, 132.11, 132.26, 156.51.

5,6-Bis[(5-methyl-1,3,4-thiadiazolyl-2-yl)sulfanylmethyl]pyrazine-2,3-dicarbonitrile (**2c**)

1.08 g (86%), *m.p.* 69–73 °C (dec.) MS *m/z* (% rel. int.): 420 (0.7), 419 (0.6), 418 (2.8, M), 302 (3.6), 288 (12.4), 287 (25.8), 286 (55.5), 132 (100). Found 418.5458, calcd. for $C_{14}H_{10}N_8S_4$ 418.5454. – IR (KBr): (2961, 2933, CH stretch), 2239 (w, CN), (1709, 1528, 1487, 1429, 1381 (s), C=C or C=N stretch) cm^{-1}. – ^1H NMR ($CDCl_3$): δ 2.70 (6 H, s), 5.00 (4 H, s). – ^{13}C NMR ($CDCl_3$): δ 16.06 (CH_3), 36.39 (CH_2), 113.06 (CN), 131.43, 156.81, 163.53, 166.61.

5,6-Bis(cyanosulfanylmethyl)pyrazine-2,3-dicarbonitrile (**2d**)

A solution of potassium thiocyanate (0.20 g, 2 mmol) in acetone (5 ml) was added dropwise to a stirred solution of **1** (0.32 g, 1 mmol) in acetone (5 ml) at ambient temperature. The suspension was stirred for 10 min, a white solid was filtered off and washed with acetone. The filtrate was evaporated to dryness, water (15 ml) was added to the solid residue. Water insoluble material was filtered off and washed with water to yield 0.26 g (95%), *m.p.* 96–98 °C. – MS *m/z* (% rel. int.): 274 (1.1), 273 (2.2), 272 (13.6, M), 215 (13.3), 214 (25.2), 213 (28.8), 188 (5.8), 187 (17.9), 186 (32.7), 59 (100). Found 271.9937, calcd. for $C_{10}H_7N_6S_2$ 271.9939. – IR (KBr): (3000, 2960, 2927, CH stretch), 2246 (w, CN), 2160 (s, SCN), (1533, 1427, 1404 (s), 1381 (s), C=C or C=N stretch) cm^{-1}. – ^1H NMR (DMSO-d_6): δ 4.85 (4 H, s). – ^{13}C NMR (DMSO-d_6): δ 34.78 (CH_2), 112.05 (SCN), 113.60 (CN), 131.45, 153.32.

Attempted cyclotetramerisations of 2a and 2b

The method, described below for the preparation of compound **6**, was used for the reactions of **2a** and **2b** with magnesium propoxide.
Product from **2a.** Black powder, 430 mg. This product was practically insoluble in pyridine and decomposed in conc. sulfuric acid with a dark brown color.
Product from **2b.** Blue-black powder, 850 mg. This solid was triturated with 2×30 ml acetone, undissolved material was filtered off and yielded 340 mg (56%) of dark powder. – UV (abs. DMSO (ε)): 340 (44 150), 650 (30 400) nm.

5,6-Bis(propoxymethyl)pyrazine-2,3-dicarbonitrile (**4**)

A solution of **1** (1.58 g, 5 mmol) in 1-propanol (25 ml) was heated under reflux for 70 h. The solvent was removed under reduced pressure, and the liquid residue was chromatographed on silica with dichloromethane. Pure compound **4** was obtained, 0.73 g (53%), liq., $R_f(CHCl_3) = 0.2$. – MS *m/z* (% rel. int.): 274 (1.3, M), 273 (1.3), 272 (1.9), 245 (2.7), 231 (2.6), 216 (4.2), 215 (1.6), 214 (5.0), 172 (37.4), 158 (52.5), 43 (100). Found 274.1423, calcd. for $C_{14}H_{18}N_4O_2$ 274.1430. – IR (film): (2965, 2937, 2878, CH stretch), 2243 (w, CN), (1735, 1461, 1385, C=C stretch), 1114 (s, C-O stretch) cm^{-1}. – ^1H NMR ($CDCl_3$): δ 0.94 (6H, t, J=7 Hz), 1.64 (4H, m), 3.53 (4H, t, J=7 Hz), 4.84 (4H, s). – ^{13}C NMR ($CDCl_3$): δ 10.52 (CH_3), 22.85 (CH_2), 70.99 (CH_2-O), 73.85 (O-CH_2-Ar), 112.86 (CN), 125.92, 131.40, 156.92.
The other chromatography fractions, which were eluted before and after the main fraction, gave 0.31 g (approx. 20%), liq. and were mixtures of three compounds, with R_f values slightly higher and equal to that of **4**.

5,6-Bis[N-(p-tolyl)aminomethyl]pyrazine-2,3-dicarbonitrile (**5a**)

A solution of **1** (0.63 g, 2 mmol) in acetone (30 ml) was slowly added to an ice-cooled solution of *p*-toluidine (0.43 g, 4 mmol) and pyridine (0.32 g, 4 mmol) in acetone (40 ml). The suspension was stirred with ice-cooling for 1 h, then at ambient temperature for 1h. The solvent was removed under reduced pressure, and water (25 ml) added to the solid residue. The yellow solid was filtered off, washed with water, triturated with diethyl ether and yielded 0.72 g, (98%), *m.p.* 197–200 °C (dec.). Recrystallisation from acetone, *m.p.* 194–196 °C (dec.). – MS *m/z* (% rel. int.): 369 (1.2), 368 (4.0, M), 263 (10.8), 262 (7.8), 261 (35.6), 260 (20.5), 259 (82.5), 107 (100). Found 368.1752, calcd. for $C_{22}H_{20}N_6$ 368.1749. – IR (KBr): 3408 (s, NH stretch), (3031, 2919, 2867, CH stretch), 2239 (w, CN), (1616, 1521 (s), 1483, 1449, C=C or C=N stretch) cm^{-1}. – ^1H NMR (DMSO-d_6): δ 2.14 (6 H, s), 4.69 (4 H, s), 5.9 (2 H, br. s), 6.61 (4 H, d, J = 8 Hz), 6.89 (4 H, d, J = 8 Hz). – ^{13}C NMR. (DMSO-d_6): δ 19.96 (CH_3), 45.69 (CH_2), 112.58 (CN), 114.18, 124.92, 129.25, 130.22, 145.43, 157.64.

5,6-Bis[4-morpholinyl]pyrazine-2,3-dicarbonitrile (**5c**)

A solution of **1** (0.32 g, 1 mmol) in acetone (20 ml) was added to a solution of morpholine (0.19 g, 2.2 mmol) and pyridine

(0.17 g, 2.2 mmol) in acetone (20 ml) at ambient temperature. The suspension was stirred for 15 min, filtered, and the filtrate evaporated at 40 °C. Water was added to the dark residue, undissolved material was filtered off and gave 0.19 g (58%), *m.p.* 140–148 °C (dec.). Chromatography on silica with acetone gave 0.12 g (37%), *m.p.* 142–144 °C (dec.). – MS *m/z* (% rel. int.): 329 (1.9), 328 (10.4, M), 241 (57.5), 183 (100). Found 328.1642, calc. for $C_{16}H_{20}N_6O_2$ 328.1648. Found 183.0546, calc. for $C_9H_5N_5$ 183.0545. – IR (KBr): (2973, 2942, 2861, 2815, CH stretch), 2245 (w, CN), (1585 (w), 1458, 1370, C=C or C=N stretch) cm^{-1}. – ^1H NMR ($CDCl_3$): δ 2.51 (8 H, t, J = 4.5 Hz), 3.69 (8H, t, J = 4.5 Hz), 4.02 (4 H, d, J = 3.9 Hz), – ^{13}C NMR ($CDCl_3$): δ 54.09, 61.43, 66.78, 112.91(CN), 125.91, 157.72 (C=O).

{29H,31H-[2,3,9,10,16,17,23,24-Octakis(propoxymethyl)-1,4,8,11,15,18,22,25-(octaza)phthalocyaninato](2-)-N^{29}, N^{30}, N^{31}, N^{32}}magnesium (**6**)

Magnesium propoxide was prepared from a mixture of magnesium (0.18 g, 7 mmol) iodine (one crystal) and 1-propanol (10 ml) flushed with nitrogen and heated under reflux for 7 h. A solution of **4** (0.50 g, 1.8 mmol) in propanol (10 ml) was added. The dark reaction mixture was heated under reflux for 8 h. The solvent was removed, water (40 ml), and glacial acetic acid (15 ml) were added. The mixture left at ambient temperature for 24 h. The dark solid was filtered off, washed with large amounts of water and then treated as above with the same amounts of water and glacial acetic acid. A dark blue solid, 0.35 g (70%) was obtained. – UV (abs. acetone (ε)): 340 (39 600), 636 (38 000) nm.

Some of this product (approx. 100 mg) was chromatographed on silica with acetone, and a middle fraction (20 mg) of a purplish blue powder was obtained. – UV (abs. acetone (ε)): 340 (48 500), 576 (11 000), 636 (62 500) nm. – IR (KBr): (2983, 2934, 2875, CH stretch), (1738, 1684, 1632, 1543, 1481, C=C or C=N stretch), 1104 (s, C-O stretch) cm^{-1}.

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