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Structural Elucidation of an Oxidation Product of Sedimentary Porphyrins by One-Pot Synthesis of 3-Methylphthalimide

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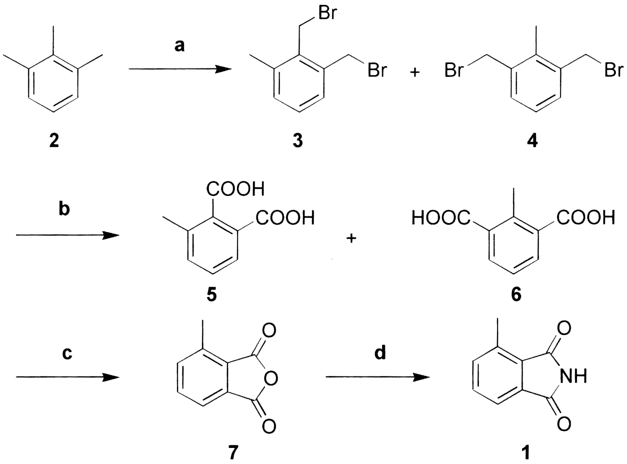
One-pot synthesis of 3-methylphthalimide was achieved from 1,2,3-trimethylbenzene. The starting compound was oxidized in two steps to produce methylphthalic acids. The *o*-isomer was converted into its anhydride, which was subjected to thermal reaction with urea to form 3-methylphthalimide. The product was identical with the reported oxidation product of sedimentary porphyrins.

Sedimentary porphyrins, first found by Treibs in 1934,[1] are usually complicated mixtures with various substituents on pyrrole or pyrroline rings as a result of diagenetic modification of precursor chlorophylls.[2] The substitution patterns can be conveniently determined after decomposition to maleimides by the chromic acid oxidation method.[3] In previously reported oxidation products of petroleum and sediments, the most abundant maleimide was usually 2-ethyl-3-methylmaleimide, which can be attributed to the predominance of 3-ethyl-4-methylpyrrole or pyrroline rings in many chlorophylls.[4,5] Barwise and Whitehead found phthalimide and an unidentified isomer of its methyl homologs in the oxidation products of porphyrins obtained from a crude oil in 1980,[6] giving the first piece of chemical evidence for the presence of sedimentary benzoporphyrins.[7] Furthermore, the discovery of methylphthalimide provided an important source of information about the precursors in diagenetic generation of benzoporphyrins. Although authentic 3- and 4-methylphthalimides are required for their identification and determination in such geological samples, no appropriate intermediate for synthesis of the former,[8] such as 3-methylphthalic acid or its derivatives, is now commercially available, and no convenient synthetic method for the compound has hitherto been reported.[9,10] In this study, we established a one-pot synthetic route to 3-methylphthalimide (**1**) from commercially available hemimellitene (1,2,3-trimethylbenzene) and determined the structure of the methylphthalimide discovered by Barwise and Whitehead.

One-pot synthesis of 3-methylphthalimide: In the synthetic path illustrated in Scheme 1, we selected all the reagents and solvents which can be evaporated, except for the one used in the final step, in order to attain a one-pot synthesis. The key step was bromination of hemimellitene (**2**), which was performed to facilitate selective oxidation of a bromomethyl in preference to a methyl group on the benzene ring. Although formation of the desired dibromide, 2,3-bis(bromomethyl)toluene (**3**), is sterically disadvantageous, the bromination gave an appreciable amount of **3**. Thus, to a solution of hemimellitene (**2**) (10 g) in carbon tetrachloride (50 mL) 2 equivalents of bromine (78 g) were added dropwise under reflux. The resulting mixture was revealed to contain dibromides **3** and **4**[11] in the ratio of 1 to 7, as analyzed with GC-MS.



Scheme 1. (a) Br_2, CCl_4, reflux; (b) 7 M HNO_3, reflux, 5 h; (c) Ac_2O, reflux, 1 h; (d) urea, 140 °C, 2 h.

The reaction mixture was evaporated to dryness under reduced pressure and the cycle of dissolution of the residue in benzene (50 mL) and evaporation to dryness was repeated five times to remove hydrogen bromide formed in the bromination. To the residual oil, 300 mL of 7 M nitric acid were added and the mixture was heated under reflux for 5 h. It was preferable to stir vigorously the reaction mixture for effective oxidation, since the dibromide otherwise stayed at the bottom of the reaction vessel. Nitric acid was evaporated under reduced pressure, and the dissolution and evaporation cycle was performed 10 times, at first using water (100 mL each) and then 5 times using benzene (50 mL each) to remove water as an azeotropic mixture.

To the oily residue, which was considered to contain methylphthalic acids **5** and **6**, acetic anhydride (50 mL) was added and the mixture was heated under reflux for an hour to give a light yellow solution. The reaction mixture was concentrated under reduced pressure and subjected to the dissolution and evaporation cycle 5 times using benzene (50 mL each). The residue was confirmed to contain 3-methylphthalic anhydride (**7**) in a separate run, in which the desired anhydride was purified by silica-gel column chromatography using benzene-ethyl acetate as eluents followed by crystallization from benzene-hexane to give needles.[12]

In the final step of the one-pot synthesis, the above-stated residue, containing **7**, was allowed to react with urea (10 g) at 140 °C for 2 h, according to the method of Muir.[13] The reaction mixture, which solidified at room temperature, was washed thoroughly with chloroform (200 mL). The precipitate was filtered off and the filtrate was applied to a silica-gel col-

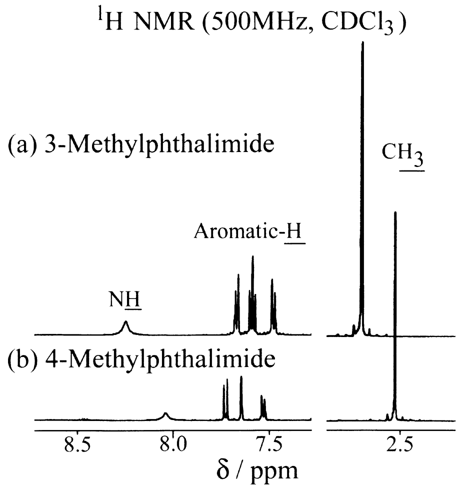


Fig. 1. ^{1}H NMR spectra of methylphthalimides.

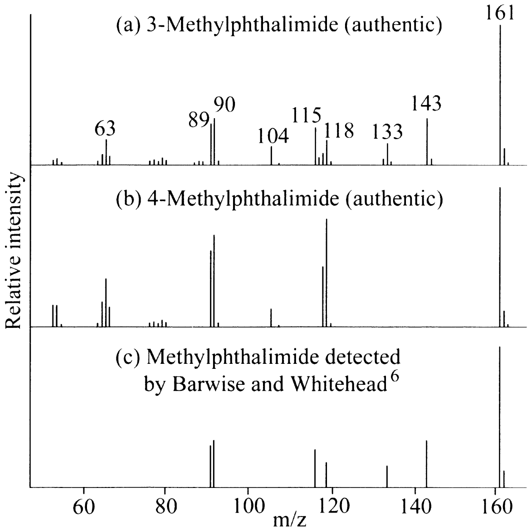


Fig. 2. Mass spectra of methylphthalimides.

umn (3 cm I.D. × 50 cm). The desired 3-methylphthalimide was eluted by chloroform–methanol (19:1) together with a by-product. This by-product could not be separated from **1** on silica-gel TLC using chloroform–methanol (19:1) as a developing solvent, and was assigned to be either 4- or 6-bromo derivative of 3-methylphthalimide,[14] as judged from MS and NMR spectra. The mixture of these phthalimides was finally separated by a silica-gel column (2 cm I.D. × 60 cm) eluting with benzene-ethyl acetate (19:1) to afford pure 3-methylphthalimide. The total yield from hemimellitene was 525 mg (3.9%). It was recrystallized from ethanol for further purification to give needles,[15] and the structure of this product was confirmed by elemental analysis and MS and NMR spectra, as shown in Figs. 1 and 2 together with those of 4-methylphthalimide.[16]

Structural elucidation of an oxidation product of sedimentary porphyrins: According to the synthetic scheme described here, 3-methylphthalimide can be easily obtained in a practical yield without using any special reagent. This work enabled definitive identification and quantification of 3-methylphthalimide in geological samples. Indeed, the above-stated methylphthalimide discovered by Barwise and Whitehead was identified as the 3-methyl isomer by comparing its mass spectrum reported with that of the authentic compound synthesized in this study (Fig. 2). We recently discovered both 3- and 4-methylphthalimides in oxidative extracts from the Neogene sediments, together with alkyl maleimides, among which 3-ethyl-4-methylmaleimide predominated. Furthermore, the isomer ratio of methylphthalimide is expected to be utilized as a maturity assessment parameter of sedimentary organic matter, similarly to methylnaphthalene or methylphenanthrene indices.[17–19] These organic geochemical investigations are now under way and will be reported elsewhere.

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11 MS data for both **3** and **4**: *m*/*z* 276, 278 and 280 (M^+), 197 and 199 ($M^+ - Br$), 118 ($M^+ - 2Br$).

12 Selected physical data for **7**: mp 104–5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (3H, s, CH_3), 7.69 (1H, d, $J = 7.6$ Hz, aromatic H), 7.79 (1H, dd, $J = 7.5$ and 7.6 Hz, aromatic H), 7.86 (1H, d, $J = 7.5$ Hz, aromatic H). Found: C, 65.89; H, 3.43%. Calcd for $C_9H_6O_3$: C, 66.67, H, 3.73%.

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14 Selected physical data for this compound: mp 235–6 °C; R_f on TLC (benzene–ethyl acetate, 9:1) 0.85; ^{1}H NMR (500 MHz, CD_3OD) δ 2.74 (3H, s, CH_3), 7.55 (1H, d, $J = 7.9$ Hz, aromatic H), 7.96 (1H, d, $J = 7.9$ Hz, aromatic H); MS: *m*/*z* 239 and 241 (M^+), 221 and 223 ($M^+ - H_2O$), 168 and 170 ($M^+ -$ CO-NH-CO), 89 ($M^+ -$ CO-NH-CO $-$ Br). Found: C, 45.36; H, 2.52; N, 5.80%. Calcd for $C_9H_6BrNO_2$: C, 45.03, H, 2.52; N, 5.84%.

15 Selected physical data for **1**: mp 193–5 °C; R_f on TLC (benzene–ethyl acetate,9:1) 0.75. Found: C, 66.62; H, 4.36; N, 8.57%. Calcd for $C_9H_7NO_2$: C, 67.07, H, 4.38; N, 8.69%.

16 4-Methylphthalimide was synthesized by the reaction of commercially available 4-methylphthalic anhydride with urea. Selected physical data for 4-methylphthalimide: mp 197–8 °C. Found: C, 67.08; H, 4.35; N, 8.90%. Calcd for $C_9H_7O_2N$: C, 67.07, H, 4.38; N, 8.69%.

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