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Studies on the tetramerization of substituted monopyrroles to type I porphyrins

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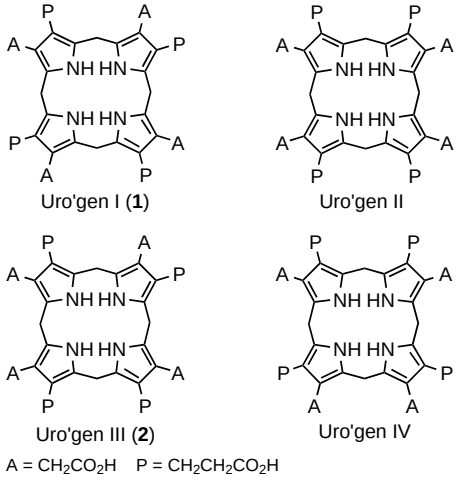
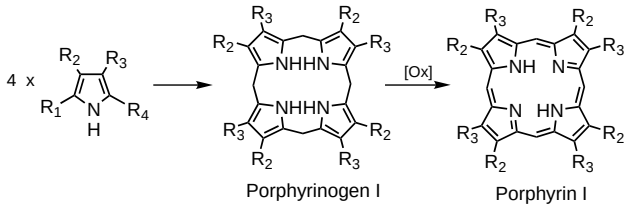
Abstract—Investigation of the tetramerization of pyrroles bearing two different electron-donating groups as substituents led to the rapid preparation under slightly acidic conditions of a porphyrin analog family with a high ratio of type I isomer for enzymatic activity studies.

Our laboratory has been involved for many years in the studies of different aspects of vitamin B_{12} biosynthesis. In order to explore the scope of activity of the first methyl transferases in the enzymatic pathways leading to B_{12}, we envisioned using analogs of uroporphyrinogen I (Uro'gen I, **1**, Scheme 1), which differs from the natural substrate Uro'gen III (**2**) by inversion of the acetate and propionate substitution on the ring D and was demonstrated to be a substrate.[1] We thought to begin our study with Uro'gen I analogs bearing substituents with one carbon longer or shorter carboxylate side-chains (Scheme 2, **3**–**7**). Since porphyrinogens oxidize easily, it is best to prepare and isolate their oxidized and more stable form, porphyrins.



Scheme 1. The four isomers of uroporphyrinogen.

Numerous works on the synthesis of type I porphyrins have been reported,[2] however, most concern the preparation of etioporphyrin I (**8**) and coproporphyrin I (**9**). Various strategies have been used, ranging from monopyrrole tetramerization to routes involving dipyrrolic, tripyrrolic or open-chain tetrapyrrolic intermediates. Since the last methods require numerous steps and we planned to prepare several uroporphyrin (Uro) I analogs, we decided to investigate the first one, which involves polymerization of four pyrroles with concomitant cyclization to porphyrinogen followed by oxidation to porphyrin (Scheme 2). This has been



10 R_1=CH_2NEt_2, R_4=CO_2H
11 R_1=CH_2OH, R_4=H

1 R_2=CH_2CO_2Me, R_3=$CH_2CH_2CO_2Me$
3 R_2=CH_2CO_2Me, R_3=$(CH_2)_3CO_2Me$
4 R_2=$CH_2CH_2CO_2Me$, R_3=$(CH_2)_3CO_2Me$
5 R_2=CO_2Me, R_3=CH_2CO_2Me
6 R_2=R_3=CH_2CO_2Me
7 R_2=R_3=$CH_2CH_2CO_2Me$
8 R_2=Et, R_3=Me
9 R_2=$CH_2CH_2CO_2Me$, R_3=Me
12 R_2=H, R_3=Me

Scheme 2. Synthesis of porphyrins I by tetramerization of monopyrroles.

Keywords: pyrroles; porphyrins; tetramerization; substituent effects.
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shown to be the method of choice for completely symmetrical porphyrins such as **6** and **7**. However, when the two β-substituents are not identical, a mixture of the four possible isomers (Scheme 1) is obtained, due to acid lability of pyrrole units at the α-position allowing cleavage followed by recombination reactions.[2a,3] Only in very special cases, for example in the presence of one very bulky or very strong electron-withdrawing group, pure type I isomers have been obtained.[2b] However, in the model studies of syntheses of etioporphyrins (**8**) and coproporphyrins (**9**), type I ratio over 90% have been reached.[4] We thought this would constitute good enough ratios for our preliminary enzymatic studies.

The monopyrroles (**10** and **11**, Scheme 2) necessary for the syntheses of the porphyrins **1**, **3** to **9** and **12** were prepared following standard published procedures. Determinations of the type I percentages were based on ^{1}H NMR or HPLC analyses, depending on the products.† The first step, porphyrinogen formation, was accomplished in absence of oxygen to avoid oxidation of intermediates, which would decrease the yields,[5] followed by oxidation in methanol under an oxygen atmosphere.

Smith et al. reported a yield of 25% pure coproporphyrin I (**9**) and 36% etioporphyrin I (**8**) containing 8% isomer contamination from pyrroles **10** bearing propionate, methyl and ethyl, methyl side-chains, respectively, in MeOH at reflux with oxidation by addition of potassium ferricyanide after 30 min.[4b] When these same conditions were used starting with pyrroles **10** bearing two electron-donating groups (EDG) as substituents [$R_2=CH_2CO_2Me$, $R_3=(CH_2)_2CO_2Me$ or $R_2=CH_2CO_2Me$, $R_3=(CH_2)_3CO_2Me$ or $R_2=(CH_2)_2CO_2Me$, $R_3=(CH_2)_3CO_2Me$], very low yields of porphyrins (less than 5%) were obtained. This result was not totally surprising as electronic effects of the substituents on pyrrolic reactivity are well known.[3b,6] Higher temperatures did improve the yields by twofold, but the relative percentage of type I isomer decreased.

Reviewing some of the other works reported, it appears that isomerization occurs both under basic or acidic conditions[7] and the highest ratios of type I obtained for etioporphyrin are at neutral or nearly neutral pH.[4a,b] Therefore, we chose to study the polymerization–cyclization of pyrroles **11** in chloroform, where the course of the reaction can be followed by ^{1}H and ^{13}C NMR by monitoring the disappearance of the methylhydroxy (~4.4 and 56 ppm) and α-free proton (~6.4 ppm) signals at room temperature. These results are presented in Table 1 (under the entry 'conditions A'). In general the reactions were rather slow, yields were moderate and the ratios of type I isomer varied from

Table 1. Formation of porphyrins

Conditions[a]	A			B			C			D[b]		
Porphyrin	Time (days)	%	% type I	Time (days)	%	% type I	Time (days)	%	% type I	Time (hours)	%	% type I
1	10	10	57	1	11	60	3	37	52	3	39	75
3	10	17	65	1	27	62	2	31	44	3	60	72
4	3	21	73	2	34	67	2	57	59	3	47	80
5	4	0	–		–			–		24	0	–
6	1	0	NA		–		2	0	NA	24	100	NA
7		–			–			–		24	65	NA
8	2	14	58	1	35	39	2	61	37	3	42	36
9	1	52	58	1	36	42	2	43	31	3	50	44
12	3	6	51		–		2	4	32	3	14	38

[a] The pyrroles **11** were formed by $NaBH_4$ reduction of the parent α-formylpyrroles (~0.2–0.4 mmol) in MeOH and used directly after work-up for the next step. In conditions A, the products were redissolved in $CDCl_3$ (500 μL) and the NMR tubes sealed under N_2. At the end of the reaction, the solvent was evaporated, the residue was resuspended in MeOH and stirred overnight under O_2. The products were isolated by preparative TLC eluted with CH_2Cl_2+1–3% MeOH. The porphyrins were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.[c] Conditions B: the reactions were run in $CHCl_3$ (1 mL) at reflux. Conditions C: the reactions were run in CH_2Cl_2 (2 mL) over Montmorillonite clay (500 mg). Conditions D: the α-hydroxymethylpyrroles **11** were dissolved in $CDCl_3$ (400 μL) or CH_2Cl_2 (800 μL) and a diluted solution of TFA in the same solvent (100–200 μL) was added. At the end of the reaction, the solution was washed with 10% aqueous $NaHCO_3$, the solvent evaporated to dryness and the residue oxidized as described before.

[b] A+x%TFA; $x=0.01$ for **1** to **5**, **8**, **9**, **12**; $x=1$ for **6** and **7**.

[c] All porphyrins prepared, but porphyrins **3** and **4**, are known compounds. Characterization data for **3** (major isomer): ^{1}H NMR δ 10.19 (s, 4H, 4 *meso H*), 5.08 (s, 8H, 4 CH_2CO_2Me), 4.12 (t, 8H, $J=7.7$ Hz, 4 $CH_2CH_2CH_2CO_2Me$), 3.75 (s, 24H, 8 CO_2CH_3), 2.75 (t, 8H, $J=6.7$ Hz, 4 $CH_2CH_2CH_2CO_2Me$), 2.65 (m, 8H, 4 $CH_2CH_2CH_2CO_2Me$); ^{13}C NMR δ 174.19, 172.03, 141.95, 132.31, 98.03, 52.40, 51.63, 33.74, 32.56, 28.14, 25.76; MS (ESI) 999 $(M+H)^+$, 100%. Characterization data for **4** (major isomer): ^{1}H NMR δ 10.26 (s, 4H, 4 *meso H*), 4.47 (t, 8H, $J=7.9$ Hz, 4 $CH_2CH_2CO_2Me$); 4.14 (t, 8H, $J=7.8$ Hz, 4 $CH_2CH_2CH_2CO_2Me$), 3.76, 3.69 (2 s, 24H, 8 CO_2CH_3), 3.34 (t, 8H, $J=7.9$ Hz, 4 $CH_2CH_2CO_2Me$); 2.78 (t, 8H, $J=6.8$ Hz, 4 $CH_2CH_2CH_2CO_2Me$), 2.64 (m, 8H, 4 $CH_2CH_2CH_2CO_2Me$); ^{13}C NMR δ 174.06, 173.60, 140.40, 138.83, 97.31, 51.72, 51.64, 37.69, 33.84, 28.67, 25.73, 21.66; MS (ESI) 1055 $(M+H)^+$, 100%.

† Integration of the *meso*-protons in the ^{1}H NMR spectra (500 MHz) provides a good estimate of the type I ratio. This was confirmed in the case of Uro I samples by HPLC analysis (silica gel column, CH_2Cl_2/MeOH, 96/4).

moderate to good. Heating does speed up the reactions and gives a slight increase in yields (Table 1, conditions B), but no better type I ratios. Another problem appears to be the lack of reproducibility of the results with important variations in reaction times, yields and type I ratios, most probably brought about by the presence of traces of acid in the solvent and/or glassware. Hence, we decided to study the effect of an acid catalyst on the reaction.

Addition of Montmorillonite clay (Table 1, conditions C) afforded better yields in a more reasonable time, but the type I ratios remained poor. The second acid catalyst studied was trifluoroacetic acid (TFA), which offers the possibility of monitoring the course of the reaction by NMR without additional work-up. Thus, it was determined that the best yields and type I ratios of porphyrin **4** were consistently obtained in the presence of 0.01% TFA. The monopyrrole **11** was completely consumed in 1 h, but the amount of porphyrin **4** was 50% higher if the work-up and oxidation were carried out after 3 h, allowing enough time for the polymerization–cyclization to porphyrinogen to reach completion before oxidation.

The conditions just described were then applied to produce our desired porphyrins (**1**, **3**–**7**) and the model porphyrins (**8**, **9**, **12**) (Table 1, conditions D). The porphyrins I bearing two different EDG substituents (**1**, **3** and **4**) were obtained in good yields with 20–28% isomer contamination. If one of the substituents was an electron-withdrawing group (**5**), no porphyrin was ever isolated under the tested conditions. Completely symmetrical porphyrins (**6** and **7**) were easily obtained in excellent yields at a concentration of TFA raised to 1%, no isomerization being possible as fragmentation/recombination of pyrroles units led to the same products. Model porphyrins (**8**, **9**, **12**) showed more susceptibility to isomerization and contamination with other isomers was greater than 50%.

In conclusion, our studies constitute the first comprehensive report on the tetramerization of pyrroles bearing two different EDG substituents for a preparative scale synthesis of porphyrins with a high ratio of type I isomer. This method represents the best and most rapid approach to prepare a porphyrin analog family for enzymatic activity studies.

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