Large-Scale Preparation of $\alpha,\beta,\alpha,\beta$ Atropoisomer of *meso*-Tetrakis(*o*-aminophenyl)porphyrin

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Summary: A 72% abundance of $\alpha,\beta,\alpha,\beta$-atropoisomer was observed in the thermal treatment of 4 g of *meso*-5,10,-15,20-tetrakis(*o*-nitrophenyl)porphyrin in 800 g of naphthalene at 130 °C. The rt reduction of the nitro groups with $SnCl_2$ and HCl followed by chromatographic separation and precipitation gives the corresponding tetrakis-$\alpha,\beta,\alpha,\beta$-amino atropoisomer in 39% yield.

The syntheses of sterically protected iron porphyrin models of natural hemoproteins include the "picket fence",[1a] pocket",[1b] and "picnic-basket"[1c] porphyrins of Collman et al., the "capped" porphyrins of Baldwin et al.,[2] the "bridged" porphyrins of Battersby et al.,[3] the "basket-handle" porphyrins of Momenteau et al.[4] and Rose et al.,[5] and the "gyroscope" porphyrins of Rose et al.[5a,6] The most frequently employed building blocks of these models are the atropoisomers of tetrakis(*o*-aminophenyl)porphyrins[1,4-6] first prepared and separated by Collman et al.[1a] Nishino et al. described elegant studies of the thermal atropoisomerism of tetrakis(2-nitrophenyl)-[7a] and -(2-(methoxycarbonyl)-5-nitrophenyl)porphyrins[7b] in toluene. However, in the first case, 500 mg of a mixture of tetrakis(2-nitrophenyl)porphyrin is dissolved in toluene and gives after equilibration and reduction of the nitro group 110 mg of the $\alpha,\beta,\alpha,\beta$-(2-aminophenyl) atropoisomer.[7a] We now report an efficient, large-scale preparation of this atropoisomer avoiding high dilution.

Crude tetrakis(*o*-nitrophenyl)porphyrin $TNPPH_2$[1d,g] (4 g) and naphthalene (800 g) were heated at 130 °C for 20 min under vigorous stirring. The hot solution was poured into a concentrated HCl solution (800 mL) at −10 °C. CH_2Cl_2 (2 L) and $SnCl_2 \cdot 2H_2O$ (39 g) were added, and the two-phase solution was magnetically stirred for 40 h at rt.[8] Almost all of the naphthalene was removed in the CH_2Cl_2 organic phase and could be recovered in 95% yield. The HCl phase was extracted twice with 100 mL of CH_2Cl_2 and neutralized slowly with NH_4OH until neutral pH. After at least five extractions (CH_2Cl_2/water) and finally another with magnetic stirring for 1 night, the mixture was chromatographed on silica gel with CH_2Cl_2 and ether (80/20), and the $\alpha,\beta,\alpha,\beta$-tetrakis(*o*-aminophenyl)porphyrin atropoisomer $TAPPH_2$ was precipitated by adding petroleum ether to the CH_2Cl_2 solution (39% yield). The yield was not good because it was difficult to extract the aminoporphyrins $TAPPH_2$ from the brown tin precipitate.

The statistic ratio $1/1/2/4 = \alpha,\beta,\alpha,\beta/\alpha^4/\alpha^2,\beta^2/\alpha^3,\beta$ of crude $TNPPH_2$ (50 mg) and naphthalene[13] (1 g) was heated at 100, 110, 130, and 150 °C under vigorous stirring, and the contents of isomers in the mixture were determined by HPLC (Table I). At 130 °C, 72% of the $\alpha\beta\alpha\beta$ isomer was observed (Figures 1 and 2). The abundance was not as good if the ratio of porphyrin to naphthalene was 1/100

Table I. Ratio of the Atropoisomers $TNPPH_2$

T (°C)	concn	$\alpha\beta\alpha\beta$	$\alpha^3\beta$	$\alpha^2\beta^2$	α^4
100	1/200	51	27	18	ϵ
110	1/200	65	21	15	ϵ
130	1/200	72	18	10	ϵ
150	1/200	68	22	11	ϵ
130	1/100[a]	46	30	24	ϵ

[a] Heterogeneous solution.

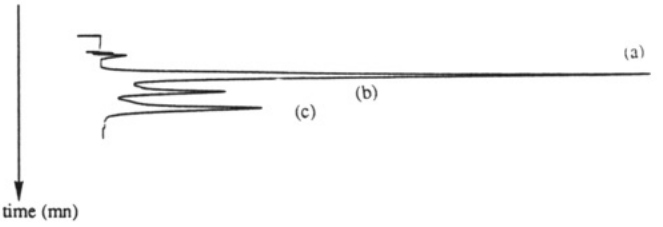

Figure 1. HPLC profiles of atropoisomeric mixture of $TNPPH_2$ after thermal treatment. Key: (a) $\alpha,\beta,\alpha,\beta$ atropoisomer $t = 4.91$ min; (b) α^2,β^2 $t = 6.46$ min; (c) α^3,β $t = 8.34$ min; the α^4 atropoisomer $t > 14$ min is not detected after 5 min of thermal treatment. Column: cyano; diameter = 4.6 mm, $h = 20$ mm, eluant: 52% to 75% THF/heptane; flow rate 1.5 mL/min, detection 420 nm; induction of the $\alpha,\beta,\alpha,\beta$ reached 65% at 100 °C and at 115 °C.

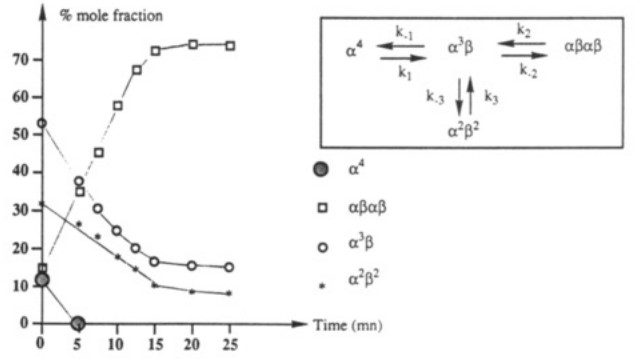

Figure 2. Thermal isomerization of the statistic ratio of crude $TNPPH_2$ at 130 °C.

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	C1	C2	C3	C4	C5	C6	Cα	Cβ	C_{meso}
$TNPPH_2\Delta$[a]	136.24	151.96	124.06	e	e	137.09	131[c]	e	115.37
$TAPPH_2$[a,f]	146.90	115.37	129.70	134.90	126.91	116.92	132.0[c]	128.43	115.93
b,f	146.93	115.55	130.08	135.02	126.63	116.65	131.6[c]	128.83	116.85
$TPPH_2$[d]	141.7	134.0	126.1	127.5	134.0	134.0	145.8[c]	130.6	119.6

[a] $CDCl_3$. [b] Me_2CO-d_6. [c] br. [d] $TPPH_2$ = tetrakis α,β,γ,δ-(phenyl)porphyrin.[12] [e] 129.81 or 131.20. [f] α,β,α,β-atropoisomer.

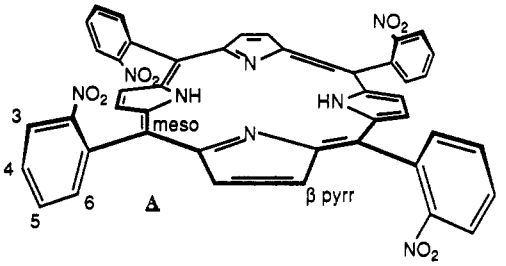

Figure 3. ^{13}C NMR data of the αβαβ $TNPPH_2$ atropoisomer A and $TAPPH_2$.

Table II. Rate Constants (k min^{-1}) and Free Energy of Activation (kJ/mol)

T (°C)	k_1	k_{-1}	k_2	k_{-2}	k_3	k_{-3}
100	0.0887	0.0042	0.0141	0.0302		
150	0.7144	0.0055	0.1420	0.4385	0.2392	0.1360

	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$
k_2	57.3	−162.6	122
k_{-2}	66.9	−130.5	119
k_1	51.4	−163.0	116
k_{-1}	3.78[a]	−316.2[a]	130

[a] These values are too difficult to obtain because the amount of the α[4] atropoisomer is too small.

Table III. 500-MHz ^1H NMR of $TNPPH_2$ and $TAPPH_2$

	H3	H4	H5	H6	H_β	NH
α,β,α,β $TNPPH_2$[a]	8.44 (m)	7.97 (m)	7.97 (m)	8.30 (m)	8.62	−2.57
b	8.43 (m)	7.98 (m)	7.98 (m)	8.37 (m)	8.66	−2.65
c	8.46 (m)	7.99 (m)	7.99 (m)	8.17 (m)	8.93	−2.34
α,β,α,β-$TAPPH_2$[a]	7.88	7.59	7.17	7.09	8.89	−2.70
α^2,β^2[a]	7.83	7.60	7.15	7.12	8.89	−2.70
α^3,β[a]	7.85	7.59	7.16	7.11	8.89	−2.70
α^4[a]	7.84	7.59	7.17	7.07	8.89	−2.70

[a] $CDCl_3$. [b] CD_2Cl_2. [c] Py-d_5.

by weight because the mixture was not homogeneous (Table I). Thermal isomerization of the α,β,α,β nitro atropoisomer was studied; the same ratio 0/72/11/17 = $\alpha^4/\alpha,\beta,\alpha,\beta/\alpha^2,\beta^2/\alpha^3,\beta$ was obtained after 20 min. Kinetic studies of the isomerization gave the first-order rate constants k and the free energy of activation $\Delta G^{\ddagger}$ using the hypothesis of Hatano et al. (Table II).[9]

It is well known that the reduction of the nitro compounds $TNPPH_2$ at 60 °C yields the amino isomers $TAPPH_2$[1d] but it is possible to do it at rt.[8] Reduction at rt for 3.5 h of the thermal isomerization product obtained at 130 °C gives the corresponding aminoporphyrins atropoisomers. But unexpectedly, a compound A (5% yield) with the highest R_f value (0.84 in CH_2Cl_2 + ε NH_3) appeared on a TLC plate in addition to the four expected amino atropoisomers which are well described in the literature.[1d] No intermediate reduction products are observed. Reduction of A at rt yielded quantitatively the α,β,α,β $TAPPH_2$ atropoisomer proving definitively that no rotation of the phenyl rings occurs at rt. ^1H and 2D-COSY NMR of this nitroisomer permitted us to assign the chemical shifts of each proton and to compare them with other NMR data (Table III).[10] By irradiation of the arene signal at the lowest field, the decoupled carbon C-2 chemical shift does not give a doublet which would be in a good agreement with a low-field signal of the H-3 proton ortho to a nitro group (Figure 3). But knowing that the ^{13}C signal of the carbon ortho to the nitro group of nitrobenzene resonates at approximately 123–124 ppm,[11] by irradiation of the 8.30 signal, the resonance at 129.81 ppm becomes a singlet without modification of the C3 carbon resonance at 124.06 ppm. This experiment definitively confirms that the H-3 proton signal resonates at 8.44 ppm. A is thus the α,β,α,β-tetranitrophenylporphyrin (Figure 3). This means that the atropoisomer A is more difficult to reduce than the other isomers.

In conclusion, the useful α,β,α,β-tetrakis(2-aminophenyl)porphyrin atropoisomer can be prepared very easily by appropriate atropoisomerization of the mixture of isomers at 130 °C in naphthalene followed by reduction at rt. The 72% abundance of the thermodynamically preferred α,β,α,β atropoisomer can be explained by dipole–dipole repulsion or by steric repulsion between the NO_2 groups through the space above the porphyrin plane.[9] This method should encourage the design and use of functional porphyrin derivatives because this minor isomer can now be prepared on a large scale in good yield.

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