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Steric and Electronic Effects of Substituents on the Yield of 5,15-Substituted Octaalkylporphines

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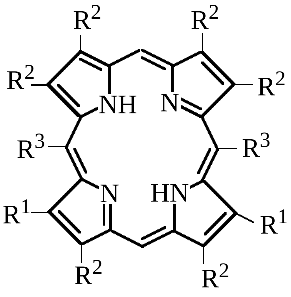
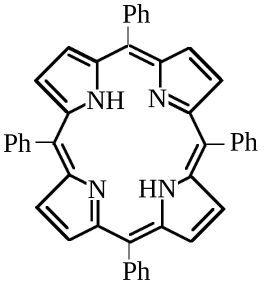
Abstract—The electronic and steric effects of peripheral substituents on the yield of 5,15-diphenyloctaalkylporphines were studied. It was found that the electronic nature of substituents in the starting benzaldehydes exerts almost no yield effect. At the same time, there is some optimal size of substituents, which provides the highest possible yield of porphyrins.

In connection with investigations into the role of porphyrins in biological systems, of great interest are 5,15-dipenyl-substituted octaalkylporphines **I**. These compounds combine merits of two the most well-understood classes of synthetic porphyrins: *meso*-tetraphenylporphyrins **II** and β-oktaalkylporphines **III**, since they are more close to natural compounds than porphyrins **II** and, in addition, may have groups amenable to modification.



I



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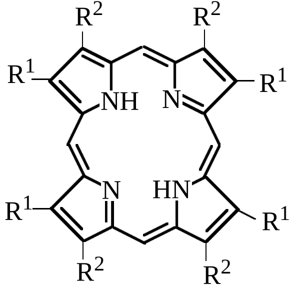
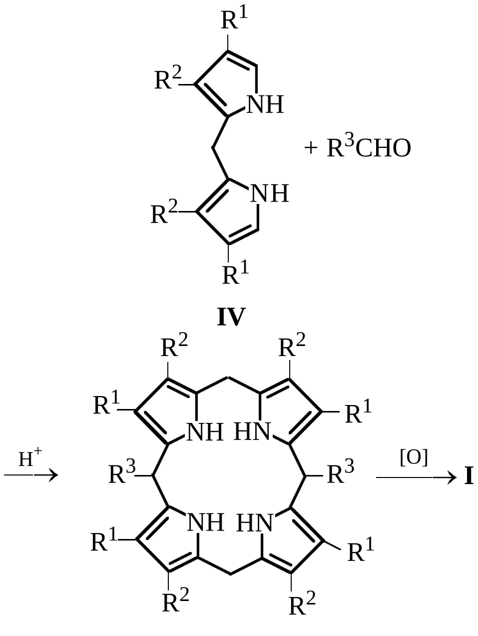


III

Earlier we developed a facile synthesis of porphyrins **I** by the condensation of tetraalkyldipyrrolylmethanes **IV** with aldehydes in chloroform in the presence of a strong organic acid to porphyrinogens **V**, followed by *in situ* oxidation of the latter with benzoquinone derivatives [1].

The aim of the present work was to study the electronic and steric effects of substituents in the β position of the starting dipyrrolylmethanes **IV** (R^1 and R^2) and aldehydes (R^3) on the yield of porphyrins **I**.



V

By the procedure described in [1] we prepared a series of porphyrins **I** having various β- and *meso*-substituents (Table 1). The starting dipyrrolylmethanes **IV** were synthesized from substituted 5-ethoxycarbonyl-2-methylpyrroles as described in [2].

By studying the steric effects of substituents in dipyrrolylmethanes (R^2) on the yield of porphyrins **I** (Table 1) we found that increase in the length of 3- and 3'-alkyl substituents in dipyrrolylmethanes **IV** has an only slight yield effect, whereas introduction of the

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Table 1. Yield and properties of 5,15-disubstituted octaalkylporphines **I**

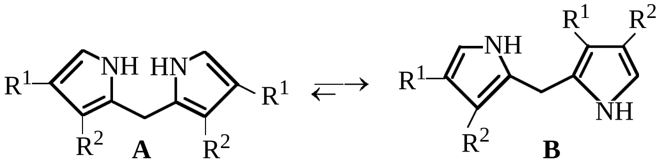
Porphyrin			Yield, %	R_f	Electronic absorption spectrum, λ_{max}, nm (log ε)					Found, %			Formula	Calculated, %		
R^1	R^2	R^3			**I**	**II**	**III**	**IV**	Soret	C	H	N		C	H	N
H	Me	Ph	61	0.23	621 (3.09)	571 (3.70)	533 (3.53)	502 (4.11)	405 (5.31)	84.0	5.6	10.4	$C_{36}H_{30}N_4$	83.4	5.8	10.8
Me	H	Ph	66	0.36	626 (3.39)	576 (3.73)	534 (357)	506 (4.14)	410 (5.27)	83.8	5.5	10.3	$C_{36}H_{30}N_4$	83.4	5.8	10.8
Me	Me	Ph	68		619 (3.03)	575 (3.82)	542 (3.70)	508 (4.19)	409 (5.29)	84.0	5.4	10.6	$C_{40}H_{38}N_4$	83.4	5.8	10.8
Me	Et	Ph	64	0.40	625 (3.46)	574 (3.92)	540 (3.82)	508 (4.28)	410 (5.40)	83.1	6.3	10.6	$C_{44}H_{46}N_4$	83.6	6.7	9.8
Me	Pr	Ph	47	0.45	625 (3.45)	574 (3.86)	540 (3.78)	508 (4.22)	409 (5.31)	83.2	8.3	8.5	$C_{48}H_{54}N_4$	83.9	7.9	8.2
Me	Bu	Ph	54	0.50	622 (3.42)	575 (3.90)	541 (3.73)	508 (4.27)	410 (5.38)	83.4	8.8	6.8	$C_{52}H_{62}N_4$	84.0	8.4	7.6
Me	Pent	Ph	41	0.55	625 (3.37)	575 (3.89)	541 (3.77)	509 (4.25)	410 (5.34)	83.8	9.0	7.2	$C_{56}H_{70}N_4$	84.1	8.8	7.1
Me	Hex	Ph	41	0.23	625 (3.19)	574 (3.68)	542 (3.56)	509 (4.04)	410 (4.97)	83.9	9.5	6.6	$C_{60}H_{78}N_4$	84.3	9.2	6.5
Me	$Ph\cdot CH_2$	Ph	23	0.36	627 (3.42)	577 (3.93)	543 (3.80)	510 (4.32)	414 (5.39)	87.9	5.8	6.3	$C_{64}H_{54}N_4$	87.4	6.1	6.4
Et	Me	Ph	43	0.66	629 (3.67)	580 (3.87)	546 (3.70)	514 (4.17)	412 (5.20)	84.2	7.3	8.5	$C_{44}H_{46}N_4$	83.7	7.4	8.9
Et	Et	Ph	46	0.40	627 (3.30)	575 (3.87)	542 (3.76)	508 (4.25)	410 (5.35)	83.4	8.2	8.4	$C_{48}H_{54}N_4$	83.9	7.9	8.2
Bu	Me	Ph	16	0.45	630 (3.69)	582 (3.89)	547 (3.72)	517 (4.13)	413 (5.21)	84.7	8.1	7.2	$C_{52}H_{62}N_4$	84.1	8.4	7.5
Me	Et	H	29	0.50	620 (3.83)	566 (3.91)	532 (4.06)	499 (4.18)	398 (5.21)	80.8	7.7	11.5	$C_{32}H_{38}N_4$	80.3	8.0	11.7
Me	Bu	H	26	0.55	620 (3.62)	567 (3.72)	534 (3.90)	498 (4.00)	400 (5.08)	81.9	8.9	9.2	$C_{40}H_{54}N_4$	81.3	9.2	9.5
Me	Bu	Me	45	0.41	623 (2.80)	583 (3.81)	551 (3.64)	514 (4.22)	413 (5.32)	81.9	9.3	8.8	$C_{42}H_{58}N_4$	81.5	9.4	9.1
Et	Et	Et	37	0.36	647 (3.20)	579 (3.79)	543 sh (3.58)	512 (4.20)	412 (5.34)	81.8	9.1	9.3	$C_{40}H_{54}N_4$	81.3	9.2	9.5
Me	Bu	Hex	21	0.66	623 (2.82)	581 (3.82)	547 (3.60)	513 (4.22)	413 (5.36)	82.9	10.2	6.9	$C_{52}H_{78}N_4$	82.3	10.4	7.4
Me	Bu	$4\text{-}NO_2\cdot C_6H_4$	52	0.27	627 (3.52)	577 (3.93)	544 (3.88)	510 (4.28)	410 (5.29)	75.7	7.0	9.7	$C_{36}H_{30}N_6O_4$	75.0	7.3	10.1
Me	Bu	$3\text{-}NO_2\cdot C_6H_4$	60	0.36	629 (3.48)	577 (3.92)	544 (3.88)	510 (4.26)	411 (5.25)	75.5	7.1	9.7	$C_{36}H_{30}N_6O_4$	75.0	7.3	10.1
Me	Bu	$2\text{-}NO_2\cdot C_6H_4$	45	0.29; 0.22	632 (3.62)	579 (3.91)	546 (3.90)	512 (4.23)	411 (5.24)	75.5	7.5	9.9	$C_{36}H_{30}N_6O_4$	75.0	7.3	10.1
Me	Bu	$4\text{-}OMe\cdot C_6H_4$	56	0.30	624 (3.60)	575 (3.89)	543 (3.75)	510 (4.26)	412 (5.39)	80.0	8.5	7.3	$C_{54}H_{66}N_4O_2$	80.8	8.3	7.0

Table 2. ^{1}H NMR spectra of 5,15-disubstituted octaalkylporphines **I**, δ, ppm

Porphyrin			NH	*meso*-H	R^1	R^2	R^3
R^1	R^2	R^3					
Me	Me	Ph	–2.76 s[a]	10.20 s	2.16 s	3.14 s	8.17 m, 7.87 m
Me	Et	Ph	–2.21 s	10.23 s	2.38 s	2.75 q, 1.08 t	8.11 m, 7.78 m
Me	Pr	Ph	–2.29 s	10.17 s	2.17 s	3.59 t, 1.75 m, 0.98 t	8.14 m, 7.90 m
Me	Bu	Ph	–2.42 s	10.17 s	2.41 s	3.91 t, 2.07 m, 1.63 m, 1.03 t	7.98 m, 7.68 m
Me	Pent	Ph	–2.37 s	10.24 s	2.46 s	3.98 t, 2.20 m, 1.72 m, 1.53 m, 0.96 m	8.08 m, 7.72 m
Me	Hex	Ph	–2.37 s	10.17 s	2.40 s	3.82 t, 2.19 m, 1.55 m, 1.46 m, 0.86 t	8.13 m, 7.77 m
Et	Me	Ph	–2.31 s	10.06 s	2.79 q, 1.08 t	3.44 s	7.94 m, 7.70 m
Et	Et	Ph	–2.37 s	10.33 s	2.77 q, 1.08 t	2.84 q, 1.08 t	8.06 m, 7.83 m
Bu	Me	Ph	–2.32 s	10.12 s	2.81 t, 1.4 m, 1.01 t	3.45 s	7.99 m, 7.72 m
Me	Et	H	–4.06 s	10.01 s	3.47 s	2.83 q, 1.08 t	–
Me	Bu	H	–3.82 s	9.91 s	3.47 s	3.92 t, 2.19 m, 1.64 m, 1.11 t	–
Me	Bu	Hex	–2.44 s	10.17 s	2.37 s	3.91 t, 2.20 m, 1.65 m, 1.06 t	2.69 t, 1.65 m, 1.42 m, 0.84 t
Me	Bu	4-$NO_2C_6H_4$	–2.49 s	10.20 s	2.27 s	3.91 t, 2.09 m, 1.63 m, 1.10 t	8.39 d, 7.96 d
Me	Bu	3-$NO_2C_6H_4$	–2.47 s	10.17 s	2.33 s	3.87 t, 2.03 m 1.66 m, 1.02 t	8.92 m, 7.77 m
Me	Bu	2-$NO_2C_6H_4$	–2.41 s	10.17 s	2.41 s	3.91 t, 2.00 m, 1.65 m, 1.06 t	8.52 m, 8.08 m, 7.77 m
Me	Bu	4-$MeOC_6H_4$	–2.49 s	10.12 s	2.42 s	3.85 t, 2.10 m, 1.67 m, 1.03 t	7.82 d, 7.14 d, 4.00 s
Me	Bu	3-$MeOC_6H_4$	–2.48 s	10.18 s	2.50 s	3.93 t, 2.14 m; 1.67 m; 1.03 t	7.61 m, 7.55 m, 3.88 s
Me	Bu	2-$MeOC_6H_4$	–2.45 s	10.19 s	2.53 s	3.99 t, 2.18 m, 1.67 m, 1.09 t	7.78 m, 7.65 m, 3.66 s

[a] With addition of trifluoroacetic acid.

bulky benzyl residue reduces the yield considerably. This result implies that bulky substituents in the 3 and 3' positions of dipyrrolylmethanes prevent formation of conformation **IVA**, which is required for condensation, and dipyrrolylmethanes are present primarily in the energetically more favorable ¨transoid conformation **IVB**.



IV

The yield of porphyrins **I** also decreases with increasing size of 4- and 4'-substituents in dipyrrolylmethanes (R^1), which is probably associated with steric hindrance to condensation.

The steric effects of substituents in aldehydes on the yield of porphyrins **I** is a more complicated case (Table 1). In going from formaldehyde to acetic aldehyde the yield of porphyrins **I** strongly increases. Further increase in the alkyl chain length (R^3 = Et) and a change to benzaldehyde only slightly affect the yield of porphyrin **I**. However, at R^3 = Hex the yield is slightly decreased, while with aldehydes with a branched alkyl chain (R^3 = *i*-Pr, *s*-hexyl) no porphyrins are formed at all, probably, by steric reasons, too.

The experimental evidence (Table 1) shows that the electronic nature of substituents and their position in the starting benzaldehydes have almost no effect of the yield of of porphyrins **I**, and only with 2,6-disubstituted benzaldehydes the yield is strongly reduced, or, in certain cases (R^3 = 2,6-$Cl_2C_6H_3$, 2,6-$Me_2C_6H_3$), porphyrins **I** are not formed at all.

It should be noted that condensations of dipyrrolylmethanes **IV** with aldehydes under the action of acids may involve, depending on conditions, rearrangement both of the starting dipyrrolylmethanes and of porphyrinogens **V** [3]. As a result, the reaction mixtures contain admixtures (1–3%) of *meso*-monosubstituted or *meso*-unsubstituted porphyrins. The yield of these by-products becomes comparable with the yield of the major product, and under certain conditions they may turn to be the only porphyrins resulting from the synthesis. However, owing to the lower polarity, the by-products are readily separable from the major products and can be identified by the hypsochromic shift of bands (by 5–10 nm) in the electronic absorption spectra.

Thus, as follows from the resulting data, the yield of porphyrins **I** is mostly affected by steric effects of substituents in the starting dipyrrolylmethanes **IV** and aldehydes; therewith, there is some optimal size of substituents, which provides the highest possible yield of porphyrins **I**.

EXPERIMENTAL

The electronic absorption spectra were measured on a Specord M-400 instrument in chloroform. The ^1H NMR spectra in $CDCl_3$ were measured on a Tesla BS-497 spectrometer at 100 MHz (internal reference HMDS) (Table 2). The purity of the products was confirmed by elemental analysis and TLC on Silufol plates (eluent benzene–heptane, 1:1). Samples for elemental analysis were dried in a vacuum for 4 h at the boiling point of toluene.

5,15-Disubstituted octaalkylporphines I. To a solution of dipyrrolylmethane **IV** {prepared from 2.3 mmol of corresponding 5,5'-bis(ethoxycarbonyl)-pyrrolylmethane by the procedure described in [1]} and 2.3 mmol of corresponding aldehyde in 200 ml of chloroform we added with stirring under CO_2 a solution of 3 mmol of chloroacetic acid in 30 ml of chloroform. The mixture was stirred in the dark for 4 h, treated with 3.5 mmol of *o*-chloranil, and heated under reflux for 1 h or left to stand for 12 h at room temperature. The solvent was removed, the residue was washed with 5% aqueous sodium hydroxide and water, and dried at room temperature until constant weight. For purification the porphyrin was dissolved in 50 ml of chloroform and subjected to chromatography first on alumina (activity grade II) and then on Silica gel L 100/250, eluent chloroform. The solvent was evaporated to 5 ml, and the porphyrin was precipitated with 30 ml of methanol, filtered off, and dried at room temperature until constant weight. The yields and properties of the resulting porphyrins are listed in Table 1.

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