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PORPHYRINS.
35.* UNUSUAL COURSE OF THE VILSMEIER REACTION WHEN FORMYLATING THE PLATINUM COMPLEX OF OCTAETHYLPORPHYRIN (revision of the known reaction)

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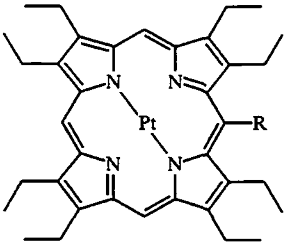
The formation of complexes of β-formyl-heptaethylporphyrin and β-(2-formylvinyl)-heptaethylporphyrin in addition to the expected mesoformylporphyrin was detected when formylating the platinum complex of actaethylporphyrin by the Wilsmeier reaction. A possible mechanism is proposed for the unusual formation of similar compounds.

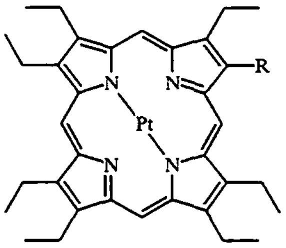
The platinum and palladium complexes of porphyrins and chlorins are of considerable interest and are used in various combinations as highly sensitive phosphorescent labels. They are applied widely as sensitive elements (sensors) in instruments for detecting oxygen and oxygen-dependent biochemical processes [2-6].

The aim of this work was to create functionalized porphyrin phosphorescent labels capable of being bound to substrates. We have therefore attempted to synthesize the platinum and palladium complexes of octaalkylporphyrins containing promising groups and a mesoformyl group by the widely known Vilsmeier reaction (for more detail see reviews in [7, 8]).

As was shown in [9], Pt complexes are the most difficult of all the metalloporphyrins to undergo the Vilsmeier reaction. Nonetheless, complex (I) was successfully obtained in very high yield (~75%) [9] by the prolonged heating (24 h) at 50°C of porphyrin (II) and the Vilsmeier complex (DMF/$POCl_3$) in dichloroethane, which is practically no different from the yields on formylating the classical copper and nickel complexes. However, the overall spectral characteristics (such as the PMR spectrum) of the isolated product were not given.



I–IV, IX, X



V–VIII, XI–XVI

I, V R = CHO; II, XIV R = H; III, XV R = $CH = N^+Me_2(OPOCl_2)^-$; IV R = CH = NMe;
VI R = CH = CH-CHO; VII R = CH_2OH; VIII R = $CH = CHCH_2OH$; IX R = $CH = N^+Me_2I^-$;
X R = CH_2NMe_2; XI R = $CH = CH\text{-}CH_2OCOCH_3$; XII R = $CHClCH_3$; XIII R = $CH = CH_2$;
XVI R = $CH = CH—CH = N^+Me_2(OPOCl)_2^-$

When repeating this reaction under the conditions given in [9] (and under other more forcing conditions) we were unable to reproduce the published results. On following the procedure of [9] precisely, the yield of complex (I) was no more than 10-25% and the yield of initial porphyrin (II) approached 50-60%. In addition, other reaction products were present in

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TABLE 1. Comparative Mass Spectra of Complexes (II) and (V)

Complex (II)			Complex (V)		
Fragment	P^{195}, m/z (%)	P^{194}, m/z (%)	P^{195}, m/z (%)	P^{194}, m/z (%)	Fragment
M^+	727 (100)	726 (73)	727 (100)	726 (66)	M^+
$[M-CH_3]^+$	712 (10)	711 (7)	712 (6)	711 (4)	$[M-CH_3]^+$
$[M-C_2H_5]^+$	698 (3)	697 (3)	699 (2)	698 (1,4)	$[M-CO]^+$
$[M-C_2H_5-CH_4]^+$	682 (4)	681 (3)	683 (0,9)	682 (1,5)	$[M-C_2H_5-CH_3]^+$
M^{2+}	363,5 (10)	363 (7)	363,5 (1,5)	363 (0,9)	M^{2+}

the reaction mixture as contaminants which differed insignificantly from complex (I) in chromatographic mobility. With the aim of optimizing the Vilsmeier reaction conditions for complex (II), we carried out the reaction at 70-75°C for 3-6 h so that the quantity of initial complex was minimal at the end of the reaction.

In order to facilitate isolation of the formylation products, the reaction mixture was treated with methylamine after isolation of the intermediate phosphorus complex (III). The aim of this treatment was to convert the portion of the reaction mixture corresponding to the formation of formylporphyrin (I) into the more polar Schiff's base (IV), which may be readily separated chromatographically from the other less polar reaction products. The following Pt complexes were isolated by column chromatography on silica gel in dichloromethane (in order of isolation): the initial complex (II), β-formylheptaethylporphyrin (V), β-(2-formylvinyl)heptaethylporphyrin (VI), and octaethylporphyrin-meso-(N-methylformaldimine) (IV) in 25-30, 10-15, 25-30, and 30-35% yield respectively. Their structures were established by PMR and mass spectra and by the synthesis of some derivatives. The corresponding alcohols (VII) and (VIII) were obtained by the reduction of complexes (V) and (VI) with $NaBH_4$ and the corresponding dimethylaminomethyl derivative (X) was obtained by treating Schiff's base (IV) with MeI and subsequent reduction of the intermediate immonium salt (IX) with $NaBH_4$. Complex (X) was also synthesized directly by reducing the phosphorus complex (III). The corresponding acetate (XI) was synthesized from alcohol (VIII) for more complete characterization of the new substances. All the compounds obtained were characterized by PMR and mass spectra. The special features of the optical spectra will be published in a separate communication.

The result obtained is the first example in porphyrin chemistry when replacement of a peripheral substituent occurred during the Vilsmeier reaction. In our opinion the formation of complexes (V) and (VI) is caused by chlorination, dehydrochlorination, devinylation, and classical formylation of the β unsubstituted and β vinylporphyrins for which no reduction in reactivity depending on the metallocomplex is observed.

Partial chlorination at the α carbon atom of an ethyl group occurs due to the low ability of porphyrin Pt complexes to react with the Vilsmeier complex at the meso position of the macrocycle on extended reaction at a relatively high temperature (70-75°C in place of 50°C). We showed previously that prolongation of the formylation reaction (for example in the synthesis of polyformylporphyrins) is linked with partial chlorination at the meso position [10], i.e., the Vilsmeier complex acts as a chlorinating agent. It is interesting that porphyrin free bases are also chlorinated only at the meso position on heating with the Vilsmeier complex [11]. Assuming that an ethyl group is subject to chlorination in the present case, the next step in the reaction may be dehydrochlorination of chloroethylporphyrin (XII) with the formation of vinylporphyrin (XIII), from which heptaethylporphyrin (XIV) may be formed by devinylation. The formation of complexes (VI) and (V) from porphyrins (XIII) and (V) from porphyrins (XIII) and (XIV) is not an unusual process. An additional argument for the generation of the intermediate vinylporphyrin (XIII) may be that the acrylaldehyde (VI) is in the trans form characteristic on formylating vinylporphyrins and chlorins [12, 13].

In order to reduce or totally exclude the hypothetical possibility of chlorination by $POCl_3$ or other chlorinating agents formed on extended heating of the Vilsmeier complex in dichloroethane, we specifically conducted numerous experiments increasing, compared with stoichiometric, the content of DMF when preparing the Vilsmeier complex over a wide time range. Complexes (V) and (VI) were formed in all cases. Even a reduction in reaction time to 1 h retained the mutual ratio of the reaction products formed.

The detection of products (V) and (VI) is not an accidental and rarely reproduced artefact of this reaction, but is a fairly regular course of the Vilsmeier reaction linked with the specific properties of the porphyrin platinum complexes. We detected no similar reactions when using palladium complexes, which are extremely similar to the platinum complexes in chemical properties.

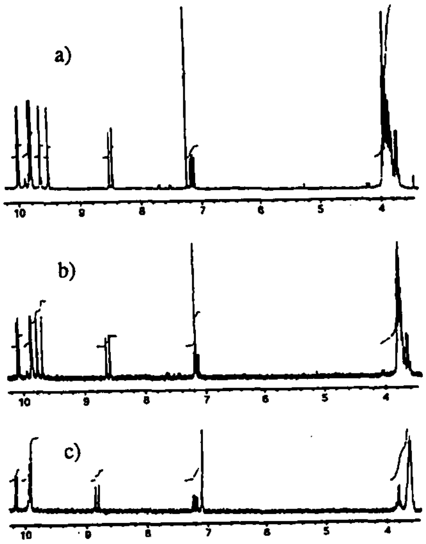

Fig. 1. PMR spectrum of complex (VI) in chloroform-D_3 at concentrations: a) 2 mg in 0.6 ml; b) 4 mg in 0.6 ml; c) 6 mg in 0.6 ml.

'In our opinion the dealkylation process on carrying out the Vilsmeier reaction was not detected previously only because complex (V) ($C_{35}H_{40}N_4OPt$, MW 727.80), one of the main reaction products, proved by coincidence to be practically identical in its mass spectrum to the initial complex (II) ($C_{36}H_{44}N_4Pt$, MW 727.85), which is shown graphically in Table 1.

The absence of Schiff's bases other than (IV) from the reaction products after treatment with methylamine is explained by the fact that phosphorus complexes of the type of (XV) and (XVI) generated in the reaction are rapidly hydrolyzed to formylporphyrins [14] by aqueous methylamine, not even being transformed into Schiff's bases.

An interesting property of acrylaldehyde (VI), in our view, proved to be the unusually strong dependence on sample concentration of signal position in the region of meso protons and methylenic protons of the ethyl substituents in its PMR spectrum. This is seen graphically in Fig. 1.

In conclusion, it must be noted that the mainly practical problem, the synthesis by known procedures of porphyrin platinum complexes, has been accomplished with the discovery of new reactions and prospects on carrying out the Vilsmeier reaction, which has been studied for a long time. It is completely possible that unexpected and real results may be obtained when carrying out the Vilsmeier reaction using porphyrin platinum complexes with other substituents.

EXPERIMENTAL

The PMR spectra were taken on a Varian 300 instrument in $CDCl_3$, the internal standard was the $CHCl_3$ signal at 7.25 ppm. The electron impact mass spectra were obtained on a Finnigan double-focussing MAT 90 instrument with an ionizing energy of electrons of 70 eV by direct insertion, the evaporating temperature for samples was 320-325°C, and the temperature of the ionizing chamber was 200°C. Masses are given for the ^{195}Pt isotope. Chromatographic separation of reaction products was carried out on columns of Merck silica gel G-60.

Formylation of Complex (II) (typical procedure). Complex (I) (100 mg), obtained in 85% yield by boiling octaethylporphyrin with an excess of $PtCl_2$ in benzonitrile, and the Vilsmeier complex, prepared from DMF (2 ml) and $POCl_3$ (2 ml), were heated at 70-75°C for 5 h in 1,2-dichloroethane (50 ml). The solvent was evaporated in vacuum, powdered ice (50 g) was added to the residue with vigorous stirring, the solid was filtered off, washed with cold water, dried, and treated with methanol (25 ml). The immonium salt (III) passed into solution and was filtered from the insoluble solid. The methanolic solution was treated with 25% aqueous methylamine solution (5 ml). After several minutes the precipitate of Schiff's base (IV) was filtered off and recrystallized from a mixture of chloroform and hexane. Bright red complex (IV) (20 mg) was obtained.

The solid formed after treating with methanol was filtered off, dissolved in chloroform (50 ml), and treated with aqueous methylamine solution (5 ml) with stirring for 10 min. The organic layer was separated, evaporated to dryness in vacuum, and chromatographed on a column (2.5 × 30) of silica gel in dichloromethane. Complex (II) (24 mg) was isolated from the first fraction, complex (V) (8 mg) from the second, complex (VI) (22 mg) from the third, and complex (IV) (6 mg) from the final fraction.

Platinum Complex of 2-Formyl-3,7,8,12,13,17,18-heptaethylporphyrin (V). PMR spectrum: 11.30 (1H, s, CHO); 10.70, 9.72, 9.71, and 9.67 (4H, all s, meso-H); 4.20 (2H, q, $\underline{CH_2}CH_3$); 3.90-3.80 (12H, overlapping q, 6 × $\underline{CH_2}CH_3$); 1.90-1.80 ppm (21H, overlapping t, 7 × $CH_2\underline{CH_3}$). Mass spectrum, m/z (%): 727 (M^+, 100); 712 ($M^+ - Me$, 10); 699 ($M^+ - CO$, 2); 363.5 (M^{2+}, 1.5).

Platinum Complex of 2-(2-Formylvinyl)-3,7,8,12,13,17,18-heptaethylporphyrin (VI). PMR spectrum: 10.16 (1H, d, J = 7 Hz, CHO); 9.96 and 9.94 (3H and 1H, all s, meso-H); 8.90 (1H, d, J = 15 Hz, $\underline{CH}{=}CHCHO$); 7.36 (1H, d d, J = 7 and 15 Hz, $CH{=}\underline{CH}CHO$); 4.12 (2H, q, $\underline{CH_2}CH_3$); 4.05-3.88 (12H, overlapping q, 6 × $\underline{CH_2}CH_3$); 1.95-1.80 ppm (21H, overlapping t, 7 × $CH_2\underline{CH_3}$). Mass spectrum, m/z (%): 753 (M^+, 100); 738 ($M^+ - Me$, 3); 725 ($M^+ - CO$, 11); 376.5 (M^{2+}, 2).

Platinum Complex of 2,3,7,8,12,13,17,18-Octaethylporphyrin-5-(N-methylformaldimine) (IV). PMR spectrum: 10.87 (1H, d, J = 1.5 Hz, $\underline{CH}{=}NMe$); 9.97 and 9.95 (2H and 1H, both s, meso-H); 3.98 (12H, q, 6 × $\underline{CH_2}CH_3$); 3.73 (4H, q, 2 × $\underline{CH_2}CH_3$); 3.99 (3H, br s, NMe); 1.92-1.82 (18H, overlapping t, 6 × $CH_2\underline{CH_3}$); 1.60 ppm (6H, t, 2 × $CH_2\underline{CH_3}$). Mass spectrum, m/z (%): 768 (M^+, 17); 738 ($M^+ - NHMe$, 100); 727 (50).

Platinum Complex of 2-Hydroxymethyl-3,7,8,12,13,17,18-heptaethylporphyrin (VII). A prepared solution of $NaBH_4$ (10 mg) in methanol (3 ml) was added rapidly to a solution of complex (V) (5 mg) in chloroform (5 ml). The mixture was stirred for 10 min until complete disappearance of the starting material from the solution, water (20 ml) was added, the mixture shaken, the organic layer was separated, and filtered through a layer (1 cm) of aluminum oxide (1 × 4 cm). The eluate was evaporated, the residue crystallized from a mixture of chloroform and methanol, and complex (VII) (4 mg) was obtained as bright red prismatic needles. PMR spectrum: 10.18, 10.04, 10.01, and 10.00 (4H, all s, meso-H); 6.03 (2H, s, $\underline{CH_2}OH$); 4.10 (2H, q, $\underline{CH_2}CH_3$); 4.00 (12H, q, 6 × $\underline{CH_2}CH_3$); 1.95 ppm (21H, t, 7 × $CH_2\underline{CH_3}$). Mass spectrum, m/z (%): 729 (M^+, 58); 713 (100); 698 ($M^+ - CH_2OH$, 17).

Platinum Complex of 2-(2-Hydroxymethylvinyl)-3,7,8,12,13,17,18-heptaethylporphyrin (VIII) was obtained analogously to complex (VII) in 90% yield. PMR spectrum: 10.12 and 9.98 (1H, 1H and 2H, all s, meso-H); 8.07 (1H, d t, J = 1 and 15 Hz, $\underline{CH}{=}CHCH_2OH$); 6.95 (1H, d t, J = 6 and 15 Hz, $CH{=}\underline{CH}CH_2OH$); 4.84 (2H, m, $\underline{CH_2}OH$); 4.12 (2H, q, $\underline{CH_2}CH_3$); 4.07-3.90 (12H, overlapping q, 6 × CH_2CH_3); 1.95-1.80 ppm (21H, overlapping t, 7 × $CH_2\underline{CH_3}$).

Platinum Complex of 2-(2-Acetoxymethylvinyl)-3,7,8,12,13,17,18-heptaethylporphyrin (XI). A mixture of complex (VIII) (5 mg), Ac_2O (0.5 ml), and pyridine (0.1 ml) in dichloromethane (5 ml) was kept for 5 h, the dichloromethane was evaporated in vacuum, and water (20 ml) was added to the residue. The precipitated solid was filtered off, and complex (XI) was obtained in quantitative yield. PMR spectrum: 10.13, 10.05, and 10.00 (1H, 1H, and 2H, all s, meso-H); 8.14 (1H, d t, J = 0.5 and 15 Hz, $\underline{CH}{=}CHCH_2OH$); 6.87 (1H, d t, J = 6 and 15 Hz, $CH{=}\underline{CH}CH_2OH$); 5.25 (2H, d d, J = 0.5 and 6 Hz, $\underline{CH_2}OH$); 4.15 (2H, q, $\underline{CH_2}CH_3$); 4.07-3.95 (12H, overlapping q, 6 × $\underline{CH_2}CH_3$); 2.30 (3H, s, COMe); 1.96-1.85 ppm (21H, overlapping t, 7 × $CH_2\underline{CH_3}$). Mass spectrum, m/z (%): 797 (M^+, 100); 739 ($M - CO_2CH_2$, 31); 727 (14).

Platinum Complex of 5-Dimethylaminomethyl-2,3,7,8,12,13,17,18-octaethylporphyrin (X). Complex (IV) (5 mg) was heated for 1 h in a mixture of dichloromethane (5 ml) and methyl iodide (0.5 ml). The solution was evaporated to dryness, the residue dissolved in dichloromethane, and a prepared solution of $NaBH_4$ (10 mg) in methanol (3 ml) was added rapidly. The solution was stirred for 10 min until complete disappearance of the starting material, water (20 ml) was added, the mixture shaken, and the organic layer separated. This solution was filtered through a layer (1 cm) of aluminum oxide (4 × 1 cm), evaporated, and complex (X) (3.5 mg) was obtained. PMR spectrum: 9.81 and 9.80 (1H and 2H, all s, meso-H); 5.55 (2H, br s, meso-CH_2); 4.10-3.90 (16H, overlapping q, 8 × $\underline{CH_2}CH_3$); 1.95-1.80 (18H, overlapping t, 6 × $CH_2\underline{CH_3}$); 1.85 (6H, s, NMe_2); 1.75 ppm (6H, t, 2 × $CH_2\underline{CH_3}$).

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