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(54) **METHOD FOR PREPARING METAL COMPLEX OF PORPHYRIN**

VERFAHREN ZUR HERSTELLUNG EINES PORPHYRIN-METALLKOMPLEXES

PROCEDE DE PREPARATION DE COMPLEXE METALLIQUE DE PORPHYRINE

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(56) References cited:
FR-A- 1 321 013 FR-A- 2 566 776
JP-A- 2 259 750 JP-A- 4 283 580
JP-A- 6 184 156 JP-A- 59 164 790
US-A- 5 192 757

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Description

TECHNICAL FIELD

5 **[0001]** The present invention relates to a process for producing metalloporphyrins. More particularly, the present invention relates to a process for producing metalloporphyrins containing transition metals inserted into the porphyrin ring which are useful as functional materials, such as photoresponsive materials and organoelectronic materials.

BACKGROUND ART

10 **[0002]** With regard to porphyrins discovered as substances involved in photosynthesis, studies are in progress on the structural control, chemical modification, and exploitation thereof as photoresponsive materials or electronic materials.

[0003] In the course of these studies, metalloporphyrins containing transition metals inserted into the porphyrin ring are gathering attention.

15 **[0004]** However, in the production of such porphyrin-metal complexes, the insertion of a transition metal ion into the porphyrin ring has been found to be difficult and because of the high temperature conditions required [a) Meumier et al. Bull. Soc. Chim. Fr. 1994, 131, 78-88. b) Collman et al. J. Am. Chem. Soc. 1995, 117, 692-703. c) Ohkubo et al. J. Mol. Cat., 1994, 91, 7-17. d) Guillard et al. J. Am. Chem. Soc. 1994, 116, 10202-10211. e) Meumier et al. Inorg. Chem. 1991, 30, 706-711. f) Saveant et al. J. Am. Chem. Soc. 1991, 113, 1586-1595. g) Quici et al. J. al. J. Mol. Cat. A: Chemical 1996, 113, 77-86] and the inert atmosphere required for conducting the reaction [a) Meumier and Momenteau et al. J. Mol. Cat. A: Chemical 1996, 113, 23-34. b) Tsuchida et al. J. Chem. Soc. Dalton Trans. 1990, 2713-2718. c) Collman et al. J. Am. Chem. Soc., 1975, 97, 1427-1439. d) Groves et al. J. Am. Chem. Soc. 1983, 105, 5791-5796.], among other restrictions, it has been impossible to synthesize transition metal-porphyrin complexes easily under mild conditions using transition metals and porphyrins in desired combinations.

25 **[0005]** FR-A-2 566 776 relates to a process for the preparation of metalloporphyrins. The process involves dissolving a tetrapyrrole compound in an aprotic solvent up to a maximum concentration of about 1 g/l. In the solution thus obtained a hydroxylated electron accepting compound which is able to complex the tetrapyrrole compound is dissolved in a molar concentration which is 100 to 1000 times the concentration of the tetrapyrrole compound. The electron accepting hydroxylated compound is for example p-nitrophenol, p-trifluoro methyl phenol, or p-trifluoro methanol. Then, a salt of the metallic cation to be inserted is added at a concentration of 10 to 100 times of the tetrapyrrole compound.

30 **[0006]** It is emphasized in FR-A-2 566 776 that the presence of the hydroxylated electron accepting compound is important to facilitate the insertion of the metallic cation into the porphyrine. Rather than anticipating or rendering obvious the present invention, FR-A-2 566 776 teaches away from the present invention.

35 **[0007]** US-A-5, 192,757 discloses cobalt porphyrins, salts or ligands thereof and their synthesis, pharmaceutical compositions and their use in controlling obesity. In its Example 2, the synthesis of a cobalt porphyrine by reaction of a solution of a porphyrine in chloroform with a solution of a cobalt acetate tetrahydrate in methanol is disclosed. No basic substance is added.

40 **[0008]** FR-A-1 321 013 relates to a process for the preparation of a cobaltprotoporphyrin by reacting a solution of protoporphyrine with a solution of cobalt salts in acetic acid in the presence of air under specific conditions, for example a pH of 2-2,5. No basic substance is added.

45 **[0009]** Therefore, an object of the present invention is to solve the problem of those prior arts and to provide a novel technology for producing metalloporphyrins by which a transition metal ion can be inserted into the porphyrin ring of an arbitrary hydrophobic or hydrophilic porphyrin compound expediently with high selectivity, for example by conducting the necessary reaction at room temperature.

DISCLOSURE OF INVENTION

50 **[0010]** Accomplished in the above state of the art, the present invention is directed, in a first aspect thereof, to a process for producing a metalloporphyrin containing a transition metal inserted into the porphyrin ring which comprises dissolving a porphyrin compound and a transition metal salt each in an independent solvent, combining the two solutions, and reacting them in the presence of 2,6-lutidine.

55 **[0011]** In connection with this first aspect, the present invention provides, in a second aspect thereof, a process for producing a metalloporphyrin wherein 2,6-lutidine is supplied in the form of the solvent for dissolving the porphyrin compound; in a third aspect, a process for producing a metalloporphyrin wherein 2,6-lutidine is added at the stage of mixing the solutions; in a fourth aspect, a process for producing a metalloporphyrin wherein said reaction is carried out at a temperature not over 40°C; in a fifth aspect, a process for producing a metalloporphyrin wherein the transition metal salt is an inorganic salt of iron (Fe) or manganese (Mn); and in a sixth aspect, a process for producing a metalloporphyrin wherein the porphyrin is an optionally substituted hydrophobic or hydrophilic porphyrin compound.

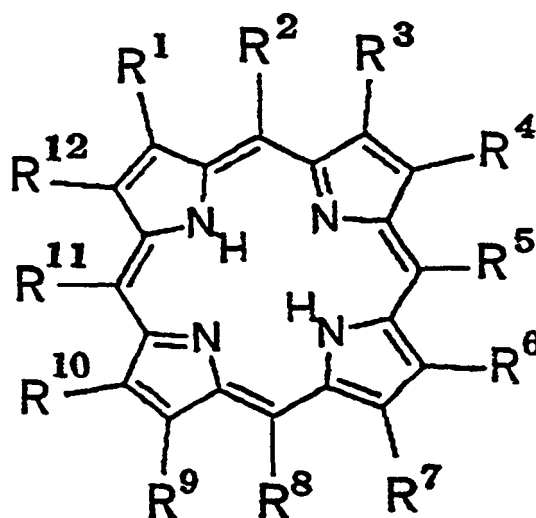
BEST MODE FOR CARRYING OUT THE INVENTION

[0012] While the present invention has the above features, its technical essence lies in enabling synthesis of various metalloporphyrins in a homogeneous reaction system under mild conditions and with high selectivity.

[0013] The working modes of the present invention are now described.

[0014] First, in the process for producing a metalloporphyrin according to the present invention, hydrophobic or hydrophilic porphyrin compounds having a porphyrin ring or rings and optionally bearing various substituent groups can be used as starting materials. These starting materials have structures permitting insertion of a transition metal ion.

[0015] The fundamental structure involved may be visualized as having a porphyrin ring of the following formula:



(wherein R¹~R¹² each represents a hydrogen atom or an organic group).

[0016] As examples of said organic group for R¹~R¹², there can be mentioned hydrocarbon groups, whether acyclic or cyclic and whether saturated or unsaturated, such as alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, etc., which may optionally be substituted by various functional groups such as halogen, hydroxy, alkoxy, alkoxy carbonyl, carboxy, amido, amino, nitro, cyano, carbamate, urea, sulfonyl, sulfenyl, phosphenyl, phosphinyl, sulfide, thioether, thioester, etc.; heterocyclic groups such as pyridyl, piperidyl, azino, azolyl, imidazolyl, triazinyl, furyl, carbazolyl, etc.; organic groups having a sugar moiety or a cyclodextrin or porphyrin ring.

[0017] Furthermore, R¹~R¹², between adjacent ones, may form a heterocycle or a carbocycle with or without the intermediary of a hetero atom or hetero atoms. The transition metal salts to be complexed with such porphyrin compounds may be any of various salts of transition metals having a valency of not less than 2. Thus, the transition metal includes but is not limited to Fe, Ni, Co, Cu, Zn, Sn, Ti, Mn, Mo, V, Zr, Cd, Ga, Sb, Cr, Nb and Al. As far as the present invention is concerned, Fe (iron) and Mn (manganese) can be mentioned as preferred transition metals.

[0018] The salt of such a transition metal may be any of various inorganic acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, etc., and various organic acids. Particularly preferred are salts of inorganic acids, such as FeCl₂ and MnCl₂.

[0019] In the process according to the present invention, said transition metal salt is preferably used in a molar excess over the starting material porphyrin. The molar ratio may for example be 1.1~30, more preferably 2~25, and still more preferably 5~20.

[0020] In conducting the reaction, the starting material porphyrin and the transition metal salt are dissolved each in an independent solvent and the resulting solutions are combined. This procedure of dissolving the porphyrin and the transition metal salt in independent solvents and combining the solutions is an indispensable requisite in carrying out the process of the present invention.

[0021] The solvent for dissolving the starting material porphyrin can be generally selected according to whether the particular porphyrin is hydrophobic or hydrophilic. Moreover, a solvent having a high solubilizing power for the porphyrin and capable of providing a homogeneous solution is selected. Taking a hydrophobic porphyrin as an example, hydrophobic organic solvents are selectively used. Thus, halogenated hydrocarbons, aromatic hydrocarbons, nitriles, etc. may be mentioned. In particular, halogenated hydrocarbons such as chloroform (CHCl₃), dichloromethane (CH₂Cl₂),

etc. constitute a preferred class of organic solvents.

[0022] On the other hand, when the starting material porphyrin is hydrophilic, hydrophilic solvents such as water, alcohols, amines, nitrogenous heterocyclic compounds, etc. can be generally employed.

[0023] The homogeneous solutions thus prepared are combined. In this combined solution, 2,6-lutidine is caused to be present. This presence of 2,6-lutidine can be assured, for example by using it as the solvent or by adding it to the combined solution, or even by using such procedures in combination.

[0024] The relative amount of the solvent and 2,6-lutidine is not particularly restricted but can be freely selected within the range assisting in the transition metal insertion reaction according to the invention and not adversely affecting the process.

[0025] The reaction temperature may generally be not over 40°C. This limit of 40°C may at times be exceeded but it does not happen that this limit is exceeded in any remarkable measure. Actually, the reaction can be conducted at room temperature or in the neighborhood thereof. In this respect, the process of the invention is basically different from the conventional processes.

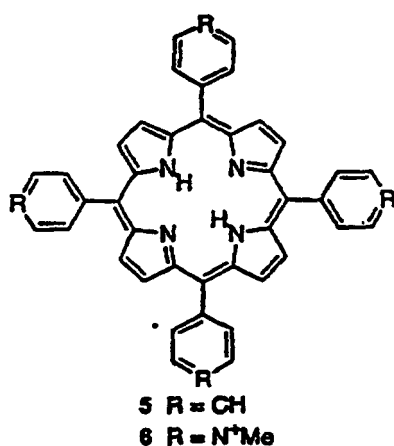
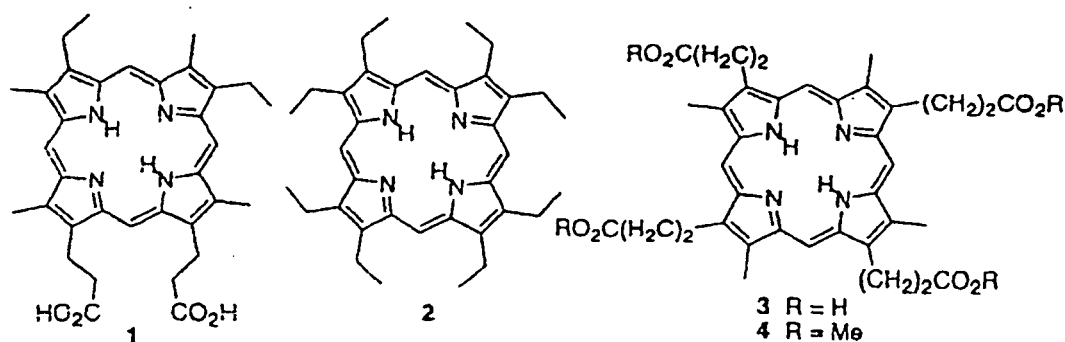
[0026] After completion of the reaction, the reaction product can be isolated and purified by various procedures such as chromatography, precipitation, recrystallization, etc.

[0027] The following examples illustrate the present invention in further detail.

EXAMPLES

[0028]

<A> In the following examples, the porphyrin compounds identified below were used as starting materials to synthesize the corresponding transition metal-porphyrine complexes.



Example 1

[0029] The hydrophobic octaethylporphyrin of the above formula (2) (16 μmol) was dissolved in chloroform (5 ml).

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Separately, FeCl₂ (260 μmol; 16 molar equivalents based on said octaethylporphyrin) was dissolved in methanol (3 ml).

[0030] The solution of octaethylporphyrin in chloroform and the solution of FeCl₂ in methanol were combined and a few drops of 2,6-lutidine was added.

[0031] The mixture was stirred at room temperature for 3 hours.

5 **[0032]** As a result, Fe was inserted into the porphyrin ring to give octaethylporphyrin-Fe complex in quantitative (100%) yield.

Example 2

10 **[0033]** Using MnCl₂ in lieu of FeCl₂, the procedure of Example 1 was otherwise followed. Here, the reaction was carried out at room temperature for 7 hours. As a result, Mn was inserted into the porphyrin ring to give octaethylporphyrin-Mn complex also in quantitative yield.

Example 3

15 **[0034]** In lieu of the octaethylporphyrin used in Example 1, the porphyrin tetramethyl ester shown above was used. This ester was dissolved in chloroform (10 ml) and the reaction was carried out under the same conditions as in Example 1.

[0035] As a result, Fe was inserted into the porphyrin ring to give coproporphyrin tetramethyl ester-Fe complex in quantitative yield.

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Example 4

[0036] MnCl₂ in lieu of the FeCl₂ was used and the reaction was carried out at room temperature for 7 hours. The procedure of Example 3 was otherwise repeated.

25 **[0037]** As a result, coproporphyrin tetramethyl ester-Mn complex was similarly obtained.

Example 5

30 **[0038]** The hydrophilic coproporphyrin of the above formula (3) (16 mmol) was dissolved in 2,6-lutidine (5 ml). On the other hand, FeCl₂ (260 μmol) was dissolved in methanol.

[0039] The above lutidine solution and FeCl₂ methanolic solution were combined and stirred at room temperature for 7 hours.

[0040] As a result, Fe was inserted into the porphyrin ring to give coproporphyrin-Fe complex in quantitative yield.

Example 6

[0041] Using MnCl₂ in lieu of FeCl₂, the procedure of Example 5 was otherwise repeated. This reaction was carried out under stirring at room temperature for 20 hours.

[0042] As a result, Mn was inserted into the porphyrin ring to give coproporphyrin-Mn complex in quantitative yield.

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Example 7

[0043] Using the hydrophilic mesoporphyrin IX of the above formula (1) in lieu of coproporphyrin, the procedure of Example was otherwise repeated.

45 **[0044]** As a result, Fe was inserted into the porphyrin ring to give mesoporphyrin IX-Fe complex in quantitative yield.

Example 8

50 **[0045]** Using MnCl₂ in lieu of FeCl₂, the procedure of Example 7 was otherwise followed. Here, the reaction was carried out under stirring at room temperature for 20 hours.

[0046] As a result, Mn was inserted into the porphyrin ring to give mesoporphyrin IX-Mn complex in quantitative yield.

Example 9

55 **[0047]** The hydrophobic tetraphenylporphyrin of the above formula (5) (16 μmol) was dissolved in chloroform (10 ml). On the other hand, MnCl₂ (260 μmol) was dissolved in methanol.

[0048] The chloroform solution and the MnCl₂ methanolic solution were combined and a few drops of 2,6-lutidine was added.

[0049] The mixed solution was stirred at room temperature for 48 hours. As a result, Mn was inserted into the porphyrin ring to give tetraphenylporphyrin-Mn complex in quantitative yield.

Example 10

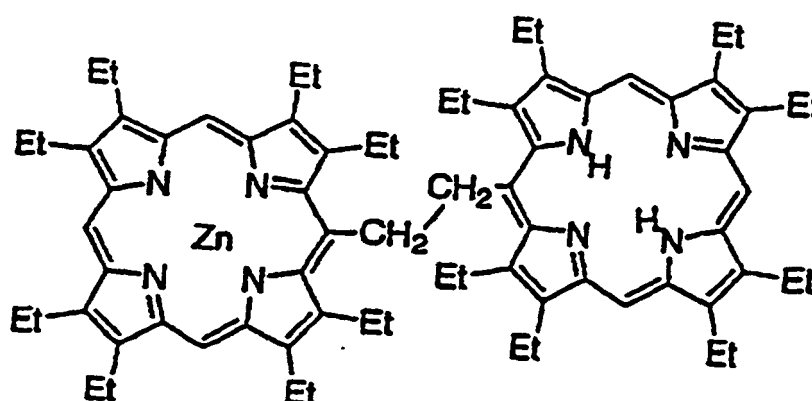
[0050] The hydrophilic tetra(N-methylpyridyl)porphyrin of the above formula (6) (16 μmol) was dissolved in water (5 ml). On the other hand, MnCl_2 (260 μmol) was dissolved in methanol (3 ml).

[0051] The above aqueous solution and MnCl_2 methanolic solution were combined and a few drops of 2,6-lutidine was added.

[0052] The mixture was stirred at room temperature for 24 hours.

[0053] As a result, Mn was inserted into the porphyrin ring to give tetra(N-methylpyridyl)porphyrin-Mn complex in quantitative yield.

 In the following examples, the dimerized porphyrin containing Zn inserted into one of the porphyrin rings as depicted below was used as the starting material.



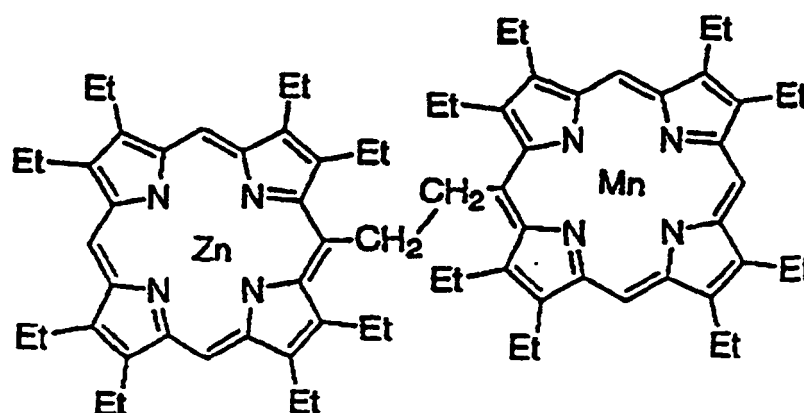
Example 11

[0054] The above porphyrin dimer-Zn complex was dissolved in chloroform. On the other hand, 16 molar equivalents of MnCl_2 was dissolved in methanol.

[0055] The two solutions were mixed and a few drops of 2,6-lutidine was added.

[0056] The reaction was conducted under stirring at room temperature for about 1 hour.

[0057] As a result, Mn was inserted into the other porphyrin ring to give porphyrin heterodimer-Zn/Mn complex of the following formula in quantitative yield.



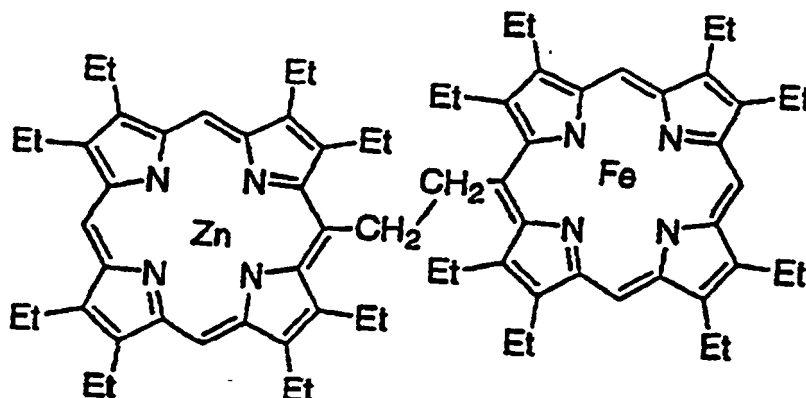
[0058] The characteristic values of this compound are as follows.

Table 1

UV-vis (CHCl_3) λ_{max} (log e) 589 (4.15), 581 (4.16),
 552 (4.19), 485 (4.66), 417 (Soret, 5.24), 370 nm (4.92);
 FAB-MS (NBA) m/z 1216 ($[\text{M}+6]^+$, 11%), 1215 ($[\text{M}+5]^+$, 27),
 1214 ($[\text{M}+4]^+$, 44), 1213 ($[\text{M}+3]^+$, 48), 1212 ($[\text{M}+2]^+$, 63),
 1211 ($[\text{M}+1]^+$, 63), 1210 (M^+ , 70), 1209 ($[\text{M}-1]^+$, 13), 613
 ($[\text{M}-\text{MnOEPCH}_2+3]^+$, 37), 612 ($[\text{M}-\text{MnOEPCH}_2+2]^+$, 31), 611 ($[\text{M}-$
 $\text{MnOEPCH}_2+1]^+$, 49), 610 ($[\text{M}-\text{MnOEPCH}_2]^+$, 35), 609 ($[\text{M}-$
 $\text{MnOEPCH}_2-1]^+$, 67), 601 ($[\text{M}-\text{ZnOEPCH}_2+1]^+$, 51), 600 ($[\text{M}-$
 $\text{ZnOEPCH}_2]^+$, 100), 599 ($[\text{M}-\text{ZnOEPCH}_2-1]^+$, 44), 598 ($[\text{M}-$
 $\text{ZnOEPCH}_2-2]^+$, 26).

Example 12

[0059] Using FeCl_2 in lieu of MnCl_2 , the procedure of Example 11 was otherwise repeated. As a result, Fe was inserted into the porphyrin ring to give porphyrin heterodimer-Zn/Fe complex of the following formula in a yield of 45%.



[0060] As a byproduct, the Fe/Fe complex containing Fe inserted into both porphyrin rings was also formed (25%).

[0061] The characteristic values of the above porphyrin heterodimer-Zn/Fe complex were as follows.

Table 2

UV-vis (CHCl_3) λ_{max} (log e) 592 (4.21), 578 (4.19),
 551 (4.31), 418 (Soret, 5.34), 363 sh nm (4.77); FAB-MS
 (NBA) m/z 1216 ($[\text{M}+5]^+$, 7%), 1215 ($[\text{M}+4]^+$, 11), 1214
 ($[\text{M}+3]^+$, 13), 1213 ($[\text{M}+2]^+$, 16), 1212 ($[\text{M}+1]^+$, 17), 1211
 (M^+ , 16), 1210 ($[\text{M}-1]^+$, 7), 615 ($[\text{M}-\text{FeOBPCH}_2+5]^+$, 15), 614
 ($[\text{M}-\text{FeOEPCH}_2+4]^+$, 21), 613 ($[\text{M}-\text{FeOEPCH}_2+3]^+$, 43), 612 ($[\text{M}-$
 $\text{FeOEPCH}_2+2]^+$, 34), 611 ($[\text{M}-\text{FeOEPCH}_2+1]^+$, 57), 610 ($[\text{M}-$
 $\text{FeOEPCH}_2]^+$, 42), 609 ($[\text{M}-\text{FeOEPCH}_2-1]^+$, 80), 608 ($[\text{M}-$
 $\text{FeOEPCH}_2-2]^+$, 17), 607 ($[\text{M}-\text{FeOEPCH}_2-3]^+$, 16), 603 ($[\text{M}-$
 $\text{ZnOEPCH}_2+2]^+$, 15), 602 ($[\text{M}-\text{ZnOEPCH}_2+1]^+$, 46), 601 ($[\text{M}-$
 $\text{ZnOEPCH}_2]^+$, 100), 600 ($[\text{M}-\text{ZnOEPCH}_2-1]^+$, 30), 599 ($[\text{M}-$
 $\text{ZnOEPCH}_2-2]^+$, 32), 598 ($[\text{M}-\text{ZnOEPCH}_2-3]^+$, 14), 597 ($[\text{M}-$
 $\text{ZnOEPCH}_2-4]^+$, 16).

INDUSTRIAL APPLICABILITY

[0062] As described above in detail, metalloporphyrins containing transition metals inserted into the porphyrin ring can be synthesized easily under mild conditions and with high selectivity in accordance with the present invention.

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Claims

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1. A process for producing a metalloporphyrin containing a transition metal inserted into the porphyrin ring which comprises dissolving a porphyrin compound and a transition metal salt each in an independent solvent, combining the solutions, and carrying out the reaction in the presence of 2,6-lutidine.

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2. The process for producing a metalloporphyrin as defined in Claim 1 wherein 2,6-lutidine is caused to be present as the solvent for said porphyrin compound.

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3. The process for producing a metalloporphyrin as defined in Claim 1 wherein 2,6-lutidine is caused to be present by adding it at the stage of combining the solutions.

4. The process for producing a metalloporphyrin as defined in any of Claims 1 - 3 wherein said reaction is carried out at a temperature not exceeding 40°C.

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5. The process for producing a metalloporphyrin as defined in any of Claims 1 - 4, wherein said transition metal is an inorganic salt of iron (Fe) or manganese (Mn).

6. The process for producing a metalloporphyrin as defined in any of Claims 1 - 5 wherein said porphyrin compound is an optionally substituted hydrophobic or hydrophilic porphyrin compound.

Patentansprüche

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1. Verfahren zur Herstellung eines Metalloporphyrins, enthaltend ein in den Porphyrinring eingeführtes Übergangsmetall, welches umfasst das Lösen einer Porphyrinverbindung und eines Übergangsmetallsalzes jeweils in einem unabhängigen Lösungsmittel, das Kombinieren der Lösungen und das Durchführen der Reaktion in Anwesenheit von 2,6-Lutidin.

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2. Verfahren zur Herstellung eines Metalloporphyrins wie in Anspruch 1 definiert, bei dem bewirkt wird, dass 2,6-Lutidin als das Lösungsmittel für die Porphyrinverbindung anwesend ist.

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3. Verfahren zur Herstellung eines Metalloporphyrins wie in Anspruch 1 definiert, bei dem bewirkt wird, dass 2,6-Lutidin anwesend ist, indem es in der Stufe des Kombinierens der Lösungen zugegeben wird.

4. Verfahren zur Herstellung eines Metalloporphyrins wie in irgendeinem der Ansprüche 1 bis 3 definiert, bei dem die Reaktion bei einer Temperatur nicht über 40°C durchgeführt wird.

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5. Verfahren zur Herstellung eines Metalloporphyrins wie in irgendeinem der Ansprüche 1 bis 4 definiert, bei dem das Übergangsmetall ein anorganisches Salz von Eisen (Fe) oder Mangan (Mn) ist.

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6. Verfahren zur Herstellung eines Metalloporphyrins wie in irgendeinem der Ansprüche 1 bis 5 definiert, bei dem die Porphyrinverbindung eine gegebenenfalls substituierte hydrophobe oder hydrophile Porphyrinverbindung ist.

Revendications

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1. Procédé de préparation de complexe métallique de porphyrine contenant un métal de transition inséré dans l'anneau de porphyrine qui comprend la dissolution d'un composé de porphyrine et d'un sel métallique de transition, chacun dans un solvant indépendant, le mélange des solutions et la réalisation de la réaction en présence de 2,6-lutidine.

2. Procédé de préparation de complexe métallique de porphyrine selon la revendication 1, dans lequel la 2,6-lutidine

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est le solvant dudit complexe de porphyrine.

3. Procédé de préparation de complexe métallique de porphyrine selon la revendication 1, dans lequel la 2,6-lutidine est ajoutée au moment de mélanger les solutions.

5 4. Procédé de préparation de complexe métallique de porphyrine selon l'une quelconque des revendications 1 à 3, dans lequel ladite réaction est réalisée à une température n'excédant pas 40°C.

10 5. Procédé de préparation de complexe métallique de porphyrine selon l'une quelconque des revendications 1 à 4, dans lequel ledit métal de transition est un sel inorganique de fer (Fe) ou de manganèse (Mn).

6. Procédé de préparation de complexe métallique de porphyrine selon l'une quelconque des revendications 1 à 5, dans lequel ledit complexe de porphyrine est un complexe de porphyrine hydrophobe ou hydrophile substitué ou non.

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