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# Porphyrins with Four Azole Substituents in *meso* Positions: X-Ray Crystal Structure of *Meso*-tetrakis-(1-benzylpyrazol-4-yl)-porphyrin at 200 K

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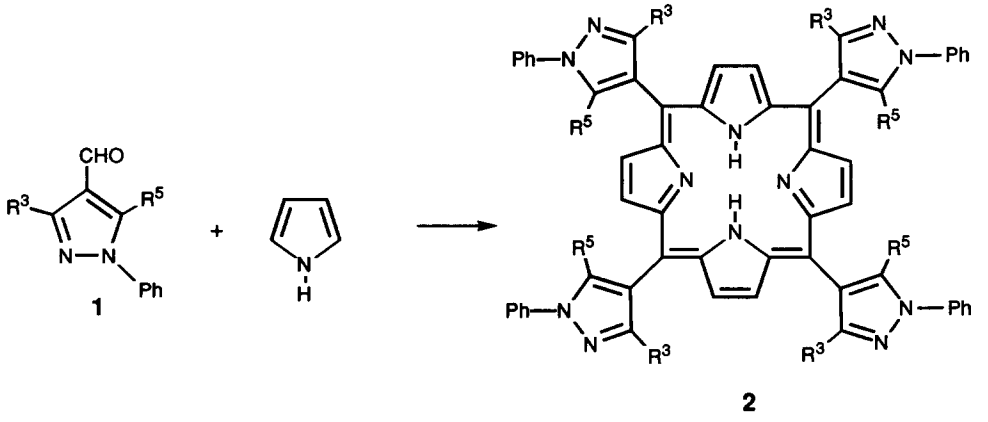
***Abstract.***—Several new porphyrins have been prepared in improved yields using an established method which was adapted to formylpyrazoles bearing on the pyrazole $N_1$-nitrogen protective groups. The deprotection of *N-para*-methoxybenzyl and SEM protected *meso*-pyrazolylporphyrins afforded the first known pyrazolylporphyrins with pyrazole free N*H* groups. The crystal and molecular structure of *meso*-tetrakis-1-(benzyl-pyrazol-4-yl)porphyrin **4a** has been solved by X-ray analysis. The porphyrin core displays a similar pattern of bond distances and angles to that of *meso*-tetraphenylporphyrin itself. The pyrazole rings are almost perpendicular to the macrocyclic ring in such a way that the nitrogen lone pairs of the pyrazole $N_2$ atoms are situated, up, down, down, up, with regard to it ($\alpha\alpha\beta\beta$ atropisomer).

## INTRODUCTION

*Meso*-substituted porphyrins are a subgroup of porphyrins with interesting structural properties.[1,2] The substituents on the *meso* positions are phenyl or substituted phenyl groups and very seldom heteroaromatic groups (pyridine derivatives have been described).[3,4] Here we will describe the case of porphyrins substituted at the *meso* positions by five-membered aromatic aza-heterocycles, that is, azoles. Amongst azoles, one of the most interesting substituents is the imidazol-2-yl group. For instance, Milgrom described the *meso*-tetrakis(imidazol-2-yl)porphyrin,[5] a compound which shows solid-state conductivity. Kobuke and Miyaji described the *meso*-bis(1-methylimidazol-2-yl)porphyrin.[6] When complexed with zinc, this compound shows a supramolecular organization forming slipped cofacial dimers.

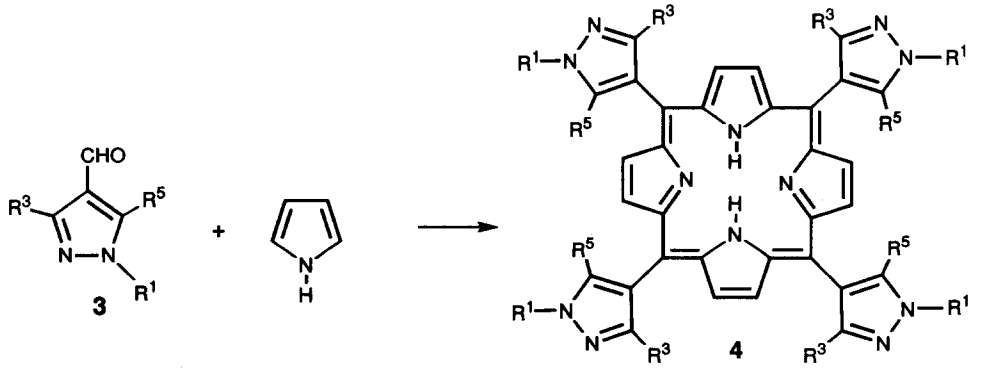
Concerning *meso*-pyrazolylporphyrins, the only described compounds (yields not reported) are *meso*-tetrakis(1,3-diphenylpyrazol-4-yl)porphyrin (**2**, $R^3$ = Ph, $R^5$ = H)[7] and its 2-nitro derivative.[8] The first one shows enhanced fluorescence quantum yields and the second one has been used to prepare copper(II) and zinc(II) complexes.




Scheme 1

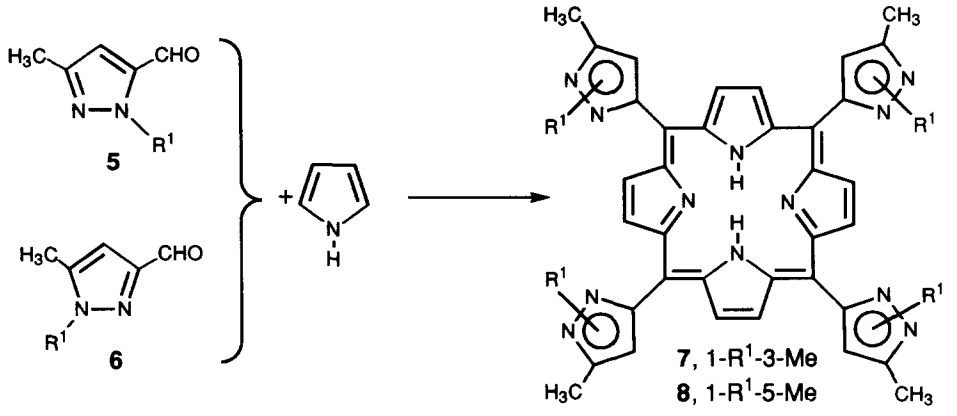
In a short communication,[9] we described the synthesis of four *meso*-tetrakis(pyrazol-4-yl)porphyrins **2** from 4-formylpyrazoles **1**: **a**, $R^3 = R^5 = H$, **b**, $R^3 = Me$, $R^5 = H$, **c**, $R^3 = R^5 = Me$ and **d**, $R^3 = Me$, $R^5 = Cl$ (Scheme 1), the substituent on the pyrazole nitrogen $N_1$ being always a phenyl group. These compounds exist as mixtures of atropisomers.

In the present work we will describe an extension of that work in two directions: the use of substituents other than the phenyl group on the pyrazole nitrogen atom, **3**, and the use of 5-and 3-formylpyrazoles, **5** and **6**, instead of 4-formylpyrazoles **1**, Schemes 2 and 3. We will also report some attempts to synthesize *meso*-tetrakis(imidazol-2-yl) and *meso*-tetrakis(benzimidazol-2-yl)-porphyrins.




**a**, $R^1 = CH_2Ph$, $R^3 = R^5 = H$
**b**, $R^1 = PMB$, $R^3 = R^5 = H$
**c**, $R^1 = PMB$, $R^3 = R^5 = Me$

Scheme 2




**a**, $R^1$=H, **b**, $R^1$=$CH_2Ph$, **c**, $R^1$=$CH_2OCH_2CH_2SiMe_3$, **d**, $R^1$=PMB, **e**, $R^1$=CO-O-Bu$^t$

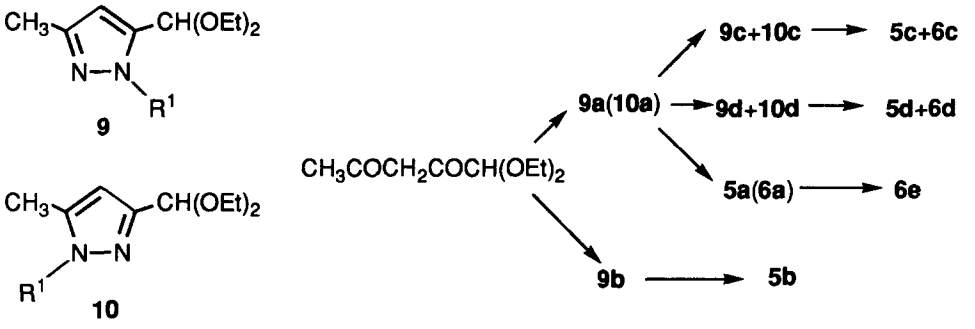
Scheme 3

Our final aim was the synthesis of porphyrins bearing at the *meso* positions four N*H*-pyrazoles. These compounds should combine the properties of the two compounds which present proton transfer in the solid state: porphyrins and *N*-unsubstituted pyrazoles. The first ones present **intramolecular** proton transfer (involving inside N-*H* protons)[10,11] and the second ones present **intermolecular** proton transfer involving several pyrazole molecules.[12,13] For this purpose, the phenyl groups of our previous synthesis were clearly unsuitable, consequently we selected groups that would remain on the pyrazole during the porphyrin synthesis (*N*-unsubstituted pyrazole aldehydes polymerize) and that could be removed afterwards. Three groups were selected (the benzyl group, although it can be cleaved,[14] was only used to study the synthetic feasability): Begtrup's *p*-methoxybenzyl (PMB),[15] 2-(trimethylsilyl)ethoxymethyl (SEM),[16] and *t*-butoxycarbonyl (BOC) groups.[17]

## RESULTS AND DISCUSSION

### Synthesis of 4- and 3 (or 5)-formylpyrazoles, 3 and 5+6.

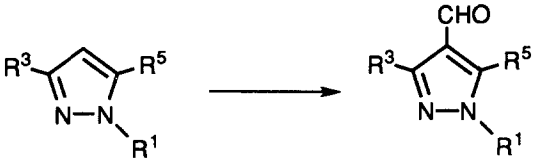
Two different approaches were used to obtain 3(5)-formyl- and 4-formyl-pyrazoles as starting materials for the syntheses of *meso*-substituted porphyrins. To synthesize the first ones, **5** (or **6**), ethyl diethoxyacetate was made to react with acetone following a known procedure which was modified changing the base used.[18,19] The resulting 1,1-diethoxy-2,4-pentanedione reacts with hydrazine hydrate to give 3(5)-methyl-5(3)-diethoxymethylenpyrazole **9a**(**10a**), whereas the reaction with benzylhydrazine gave regioselectively the 1-benzyl-3-methyl-5-diethoxymethylene derivative **9b**. Starting from **9a**(**10a**) the mixture of SEM protected acetals, **9c**+**10c**, was obtained which could be hydrolyzed to the corresponding aldehydes **5c**+**6c** ($R^1$ = SEM). Similarly, the *N*-substitution of **9a**(**10a**) with *p*-methoxybenzyl chloride (PMBCl) gave a mixture of both possible isomers **9d** and **10d**. The acetals **9b** and the mixture of **9d** and **10d** were hydrolyzed with dilute hydrochloric acid to give the corresponding aldehydes **5b** ($R^1$= $CH_2Ph$) and the **5d**+**6d** mixture ($R^1$ = PMB) in good yields (Scheme 4). Reaction of **5a**(**6a**) with di-*tert*-butyldicarbonate affords only the **6e** isomer ($R^1$ = BOC). Since the final purpose was to cleave off the protecting groups, we were not interested in separating the mixtures **5**/**6**, nor the resulting porphyrins **7**/**8**.




**a**, $R^1$ = H, **b**, $R^1$ = $CH_2Ph$, **c**, $R^1$ = $CH_2OCH_2CH_2SiMe_3$, **d**, $R^1$ = PMB, **e**, $R^1$ = CO-O-$Bu^t$

Scheme 4

4-Formylpyrazoles **3a**, **3b** and **3c** were prepared in two steps; first, using β-dicarbonyl compounds and benzylhydrazine or *p*-methoxybenzylhydrazine to obtain the pyrazoles **11a**, **11b** and **11c** which were, in a second step, formylated under Vilsmeier-Haack conditions (scheme 5). Compound **11a** was also obtained by alkylation of pyrazole with benzyl chloride under phase transfer conditions (PTC) without solvent.



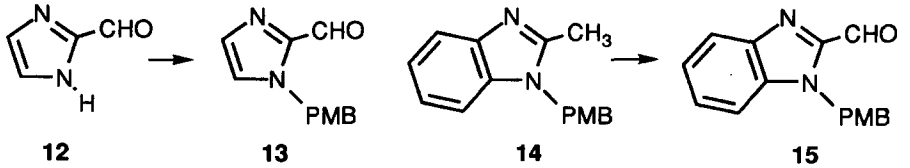

**11**, **a**, $R^1$ = $CH_2Ph$, $R^3$=$R^5$=H
**b**, $R^1$ = PMB, $R^3$=$R^5$=H
**c**, $R^1$ = PMB, $R^3$=$R^5$=Me

**3**, **a**, $R^1$ = $CH_2Ph$, $R^3$=$R^5$=H
**b**, $R^1$ = PMB, $R^3$=$R^5$=H
**c**, $R^1$ = PMB, $R^3$=$R^5$=Me

Scheme 5

**Synthesis of 2-formylimidazoles and 2-formylbenzimidazoles**

1-*p*-Methoxybenzyl-2-formylimidazole **13** was prepared from 2-formylimidazole **12** and *p*-methoxybenzylchloride (Scheme 6). 1-*p*-Methoxybenzyl-2-formylbenzimidazole **15** was prepared in two steps in good yields using commercial 2-methylbenzimidazole as starting material. The protection of the N*H* group was achieved with *p*-methoxybenzyl chloride under PTC and the intermediate product **14** was oxidized with selenium dioxide to give **15**.




**12** **13** **14** **15**

Scheme 6

## Synthesis of *meso*-tetrakis-pyrazolylporphyrins

From the two established methods existing for porphyrin synthesis via the tetra-cyclization of aldehydes and pyrrole only the method of Adler and Longo[20] had been reported to yield pyrazole substituted porphyrins.[7,9] Since this method gives only very moderate yields, has a tedious workup procedure and uses rather inconvenient solvents, *i. e.* propionic acid and nitrobenzene, it was desirable to investigate the scope of the other described method developed by Lindsey and coworkers.[21] With slight variations concerning temperature and reaction time it was possible to obtain a number of *N*-protected *meso*-substituted porphyrins in improved yields compared to the earlier employed method.[9] Furthermore the workup procedure was simplified allowing the synthesis and purification of porphyrins in a scale of up to 15-20 mmol starting material in two days. Following this procedure a variety of porphyrins can be prepared provided the starting aldehyde is sufficiently soluble in dichloromethane.

In a first attempt to synthesize *meso*-tetrakispyrazolylporphyrins, the pyrazole derivative **5b** was used as free aldehyde. The obtained porphyrin **7b** showed a rather complicated proton spectrum due to the existence of four different atropisomers. It was not possible to separate these isomers as the rotation barrier for the pyrazole rings is too low and rapid isomerization occurs at room temperature. A rather unusual high field shift observed for the benzylic protons is probably due to an interaction with the aromatic macrocycle as the model compound **18** with a phenyl ring does not show a similar effect (see NMR study of porphyrin **7b**).

The SEM-protected porphyrins **7c+8c** were synthesized from the mixture of aldehydes **5c+6c.** The $^1$H NMR spectrum shows the internal pyrrole NH protons at -2.88 ppm, as usual in porphyrins.The remaining signals can be easily interpreted as coming essentially from isomer **8c**. From the reaction of pyrrrole with the isomeric mixture **5d+6d**, the corresponding porphyrins **7d+8d** were obtained in a 11 % yield. Because of the two differently substituted aldehydes the spectra of this compound were even more complicated than those of the molecule **7b**. Therefore the interpretation (see experimental part) was done in a simplified way.

The reaction of 4-formylpyrazole **3b** with pyrrole gave the corresponding porphyrin **4b** in 14 % yield which is an improvement of 100 % in comparison to the very similar compound synthesized previously (**2a**) (phenyl instead of PMB, 7.3 % yield).[9] Likewise, from 4-formylpyrazole **3a** the porphyrin **4a** was obtained and its X-ray structure determined ($\alpha\alpha\beta\beta$ atropisomer, see X-ray crystallographic study). Porphyrin **4c** having not been isolated pure will not be described.

Along the sequence of reactions involved, the proportions of pyrazole isomers are modified during the purification procedures. Here is a summary of these sequences: **9c** (36 %) + **10c** (64 %) → **5c** (33 %) + **6c** (67 %) → **7c** (<5 %) + **8c** (>95 %); **9d** (40 %) + **10d** (60 %) → **5d** (37 %) + **6d** (63 %) → **7d** (20 %) + **8d** (80 %).

## Attempted synthesis of imidazole and benzimidazole substituted porphyrins

2-Formylimidazole **12** was used in an experiment to obtain an already described porphyrin.[5] As the starting material was practically insoluble in dichloromethane no porphyrin was obtained. Using the procedure described for formylpyrazoles, 1-*p*-methoxybenzyl-2-formylimidazole **13** did not afford the corresponding porphyrin, instead the starting material was recovered. 1-*p*-Methoxybenzyl-2-formylbenzimidazole **15** was chosen as starting material to prepare benzimidazolyl-porphyrins. However this compound, as well as the *N*-unprotected imidazole **12**, did not give the desired compound but a very complex mixture of products. After chromatographic separation (flash column and preparative thin layer chromatography) none of the fractions showed the characteristic Soret band (420 nm) and no further identification of the mixtures was attempted.

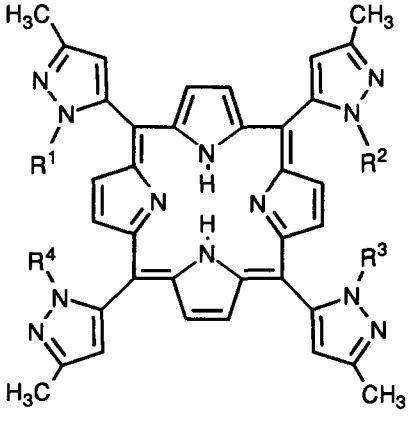
**Deprotection of *N*-1-substituted porphyrins**

The yield in the BOC protected aldehyde **6e** being very low, the synthesis of the corresponding porphyrin was not attempted. Thus the deprotection experiments were carried out on PMB and SEM protected porphyrins.

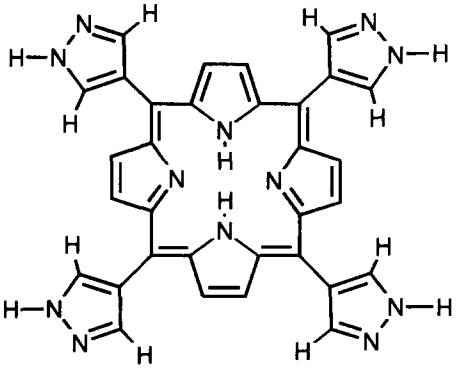
*a) Deprotection of* N-*1*-p-*methoxybenzyl substituted porphyrins* (PMB-porphyrins)

Two different reagents were employed to cleave the 1-*p*-methoxybenzyl group used to protect the N-*H* of the pyrazole aldehydes. In a first attempt, cerium (IV) ammonium nitrate (CAN) was chosen as it had been reported to be a mild and effective cleaving agent for *N*-PMB-protected heterocycles.[22,23] As the obtained product of the reaction of porphyrin **4b** with CAN (possibly the cerium complex of the corresponding porphyrin) was very unsoluble in most solvents it was not possible to determine whether the protecting groups were removed (structure **17**) or not.

Trifluoroacetic acid (TFAA) had been used for the deprotection of PMB groups in a variety of examples.[24] The procedure and the treatment of the products are very simple and the yield is rather good. This way, by treatment of **7d+8d** with TFAA, several milligrams of unprotected porphyrin **16a** (identical to **7a/8a**) were obtained which showed a very simple proton spectrum as neither isomerism (when the substituent on the pyrazole nitrogen is a proton, tautomerism makes both isomers equivalent) nor atropisomerism are present.



**16**



**17**

**a**, $R^1 = R^2 = R^3 = R^4 = H$

**b**, $R^1 = R^2 = R^3 = CH_2OCH_2CH_2Si(CH_3)_3$, $R^4 = H$

*b) Deprotection of* N-*[2-(trimethylsilyl)ethoxy]methyl substituted porphyrins* (SEM-porphyrins)

The SEM group was selected because it is a good protecting group, easy to remove under mild and selective conditions.[16] Thus, hydrolysis of the pyrazole acetals to pyrazole aldehydes was achieved while the protecting group remained. Moreover in the second step, porphyrins bearing the SEM substituent could be prepared.

Two different reagents were used to cleave the SEM group. The treatment of **8c** with 3N aqueous HCl at reflux for 2 h afforded the partly deprotected porphyrin **16b**, while 17 h reflux yielded the totally deprotected porphyrin **16a**, identical to that obtained from **7d+8d**. When TFAA was used for the deprotection of **8c**, the expected porphyrin **16a** was obtained in good yield. Both methods are comparable in procedure and in yields.

## X-Ray Crystallographic Study

The molecule of porphyrin **4a** was located on a crystallography symmetry center and its molecular structure, as projected on the mean plane of the macrocycle, is displayed in Fig. 1a.[25] The two independent pyrazole rings are tilted up (U) and down (D) with respect to that plane giving rise to a global conformation UDDU, Table 1 (these conformations are called $\alpha\alpha\beta\beta$).[9] The porphyrin core is slightly distorted from planarity, the angles between the pyrrole ring with a hydrogen (i = 2) and without it (i = 1, Fig. 1a) and between them and those of the contiguous *meso* carbon atoms are 3.8(1)°, 2.2(1)° and 3.1(1)° respectively (Fig. 1b).

The geometry of the porphyrin core, in terms of bond distances and angles, exhibits a good agreement with that of *meso*-tetraphenylporphyrin:[26] similar C-$C_{meso}$ distances, peripheral C-C bonds opposite to the imino nitrogen (N101) and $C_\alpha$-$C_\beta$ distances (Ci02-Ci03, Ci04-Ci05) shorter and longer than the corresponding to the other independent pyrrole ring (Table 1). The internal bond angle at the imino nitrogen (*i.e.* the 'pyridine-like' nitrogen) is smaller than that of the amino one (*i.e.* the 'pyrrole-like' N-H nitrogen).

Only a few structures other than *meso*-tetraphenylporphyrin have been retrieved from the Cambridge Structural Database (CSD hereinafter)[27] displaying hydrogen atoms, neither disorder nor error, R < 0.075 and aromatic rings at the *meso* positions: tetrakis(*p*-chlorophenyl)porphyrin (CSD refcode: WASPEL),[28] octaphenylporphyrin (CSD refcode: HAYBOY),[29] and dodecaphenylporphyrin (CSD refcode: LADGAY),[30] whose geometries are gathered in Table 1. The pattern of bond distances in the porphyrin core reflects the following influence of substituents. The chlorine atom at *para* position of the *meso*-phenyl ring breaks the symmetry of the pyrrole rings and both C-$C_{meso}$ bonds appear to be different without affecting the angles at the imino and amino nitrogen atoms. The substitution of the C-hydrogen atoms of the pyrrole rings by phenyl groups mainly affects the bond opposite to the nitrogen atoms ($C_\beta$-$C_\beta$), moreover the $C_\alpha$-$C_\beta$ and C-$C_{meso}$ bonds are longer than the corresponding ones in the unsubstituted porphyrins. The internal bond angle at the nitrogen atoms provides information about the location of the N-H hydrogen atom attached to one of them as well as on the disorder presented by some porphyrins in a similar way to that reported for NH-pyrazoles.[31]

The four pyrazole rings in **4a** present Paul-Curtin's coordinates[31] of $\Delta A(N)$ = 7.6-7.7° and $\Delta R(NC)$ = 1.6-1.9 x $10^{-3}$ Å, very close to the group of *N*-methylpyrazoles [$\Delta A(N)$ = 7.2° and $\Delta R(NC)$ = 1.8 x $10^{-3}$ Å],[31] thus they can be described as 'standard' *N*-alkylpyrazoles.Besides the intramolecular N-H···N bonds, characteristic of porphyrins, the molecules of **4a** are linked by weak C-H···N interactions as well as by additional weak C-H···$\pi$ electronic cloud interactions (Table 1).[32]

Due to the absence of substituents on the pyrazole carbons ($R^3$ = $R^5$ = H) near the *meso* bond, the rotational barrier of porphyrin **4a** is too low and this compound does not show atropisomerism in solution.

## NMR Study of the Atropisomerism of Porphyrin 7b

Aryl *meso*-substituted porphyrins can exist in four atropisomers: $\alpha\alpha\alpha\alpha$, $\alpha\alpha\alpha\beta$, $\alpha\alpha\beta\beta$ and $\alpha\beta\alpha\beta$:

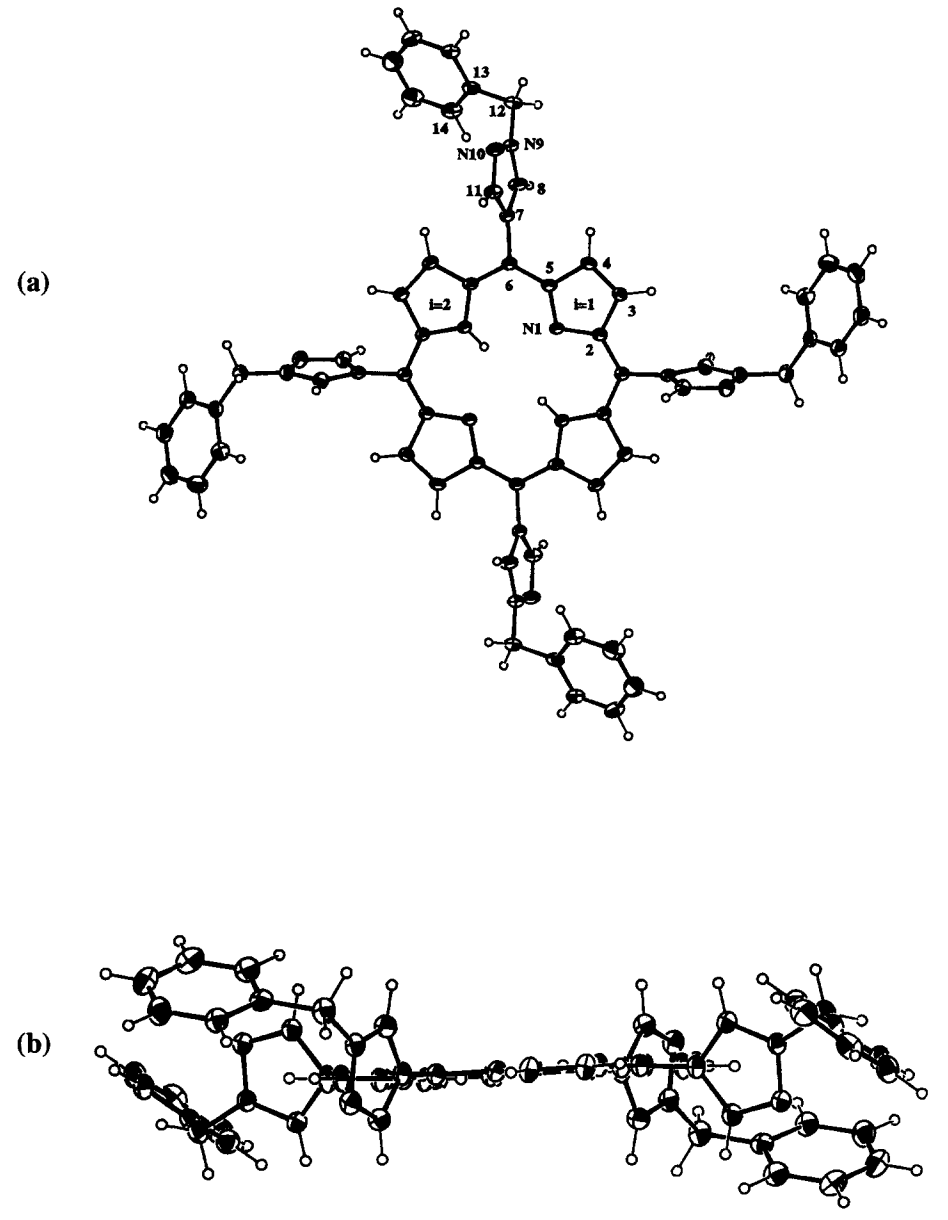



**Fig. 1.** Two perspective views of the molecular structure of porphyrin **4a** showing the atom labelling [**i=1**, **N10** means **N(i01)** or **N(101)** in Tables 1 and 5]. The ellipsoids show 30% occupancy.

**Table 1.** Selected geometrical parameters (Å,°). Dash stands for (1-x, 1-y, 1-z) symmetry operation and C(A), C(B), C(C), C(D) for the centroids of the C113...C118, N201...C205, N101...C105 and C207...C211 rings. CSD refcodes: TPHPOR01=tetraphenylporphyrine, WASPEL=tetrakis(p-chlorophenylporphyrine, HAYBOY=octaphenylporphyrin and LADGAY =dodecaphenylporphyrin, see text for references.

| a) Porphyrin core | Present work | | TPHPOR01 | | WASPEL | | HAYBOY | | LADGAY | |
|---|---|---|---|---|---|---|---|---|---|---|
| | i=1 | i=2 | i=1 | i=2 | i=1 | i=2 | i=1 | i=2 | i=1 | i=2 |
| N(i01)-C(i02) | 1.371(3) | 1.377(3) | 1.369 | 1.377 | 1.376 | 1.364 | 1.368 | 1.361 | 1.366 | 1.366 |
| C(i02)-C(i03) | 1.455(4) | 1.419(3) | 1.454 | 1.424 | 1.427 | 1.450 | 1.438 | 1.444 | 1.464 | 1.449 |
| C(i03)-C(i04) | 1.342(3) | 1.359(4) | 1.347 | 1.353 | 1.355 | 1.348 | 1.332 | 1.375 | 1.368 | 1.405 |
| C(i04)-C(i05) | 1.450(4) | 1.422(3) | 1.453 | 1.432 | 1.445 | 1.433 | 1.443 | 1.436 | 1.464 | 1.449 |
| C(i05)-N(i01) | 1.369(2) | 1.373(3) | 1.359 | 1.370 | 1.380 | 1.376 | 1.376 | 1.379 | 1.366 | 1.366 |
| C(i05)-C(i06) | 1.399(3) | 1.399(3) | 1.399 | 1.402 | 1.403 | 1.391 | 1.399 | 1.407 | 1.410 | 1.414 |
| C(i06)-C(i07) | 1.486(3) | 1.489(3) | 1.505 | 1.502 | 1.487 | 1.497 | 1.495 | 1.487 | 1.496 | 1.496 |
| C(i06)-C(202/102') | 1.398(4) | 1.397(2) | 1.395 | 1.400 | 1.385 | 1.410 | 1.413 | 1.401 | 1.414 | 1.410 |
| C(i02)-N(i01)-C(i05) | 105.6(2) | 109.7(2) | 106.2 | 109.2 | 106.2 | 109.2 | 105.4 | 110.9 | 105.9 | 112.1 |
| N(i01)-C(i02)-C(i03) | 110.3(2) | 107.1(2) | 110.2 | 107.4 | 110.0 | 107.3 | 110.4 | 107.1 | 110.7 | 106.7 |
| C(i02)-C(i03)-C(i04) | 106.7(3) | 108.0(2) | 106.3 | 107.9 | 107.6 | 107.9 | 107.1 | 107.3 | 106.2 | 107.3 |
| C(i03)-C(i04)-C(i05) | 106.9(2) | 108.5(3) | 107.0 | 108.2 | 106.8 | 107.8 | 107.3 | 108.4 | 106.2 | 107.3 |
| N(i01)-C(i05)-C(i04) | 110.5(2) | 106.7(2) | 110.2 | 107.4 | 109.4 | 107.9 | 109.8 | 106.3 | 110.7 | 106.7 |
| C(i07)-C(i06)-C(202/102') | 115.9(2) | 119.1(2) | 116.4 | 118.2 | 117.8 | 116.9 | 118.7 | 115.5 | 116.4 | 120.6 |
| C(i05)-C(i06)-C(i07) | 118.9(2) | 115.3(2) | 118.0 | 116.2 | 117.4 | 117.3 | 115.2 | 118.5 | 120.6 | 116.4 |
| C(i05)-C(i06)-C(202/102') | 125.2(2) | 125.5(3) | 125.6 | 125.5 | 124.9 | 125.8 | 126.2 | 125.9 | 123.0 | 123.0 |

b) Substituents

| | i=1 | i=2 | | i=1 | i=2 |
|---|---|---|---|---|---|
| C(i07)-C(i08) | 1.369(4) | 1.371(4) | C(i06)-C(i07)-C(i08) | 127.6(2) | 128.4(3) |
| C(i08)-N(i09) | 1.349(3) | 1.346(3) | C(i06)-C(i07)-C(i11) | 128.7(3) | 127.7(3) |
| N(i09)-N(i10) | 1.340(3) | 1.344(3) | C(i08)-C(i07)-C(i11) | 103.6(2) | 103.8(3) |
| N(i10)-C(i11) | 1.330(3) | 1.330(3) | C(i07)-C(i08)-N(i09) | 107.7(2) | 107.6(3) |
| C(i11)-C(i07) | 1.395(4) | 1.398(4) | C(i08)-N(i09)-N(i10) | 111.9(2) | 112.0(3) |
| N(i09)-C(i12) | 1.463(3) | 1.467(3) | N(i09)-N(i10)-C(i11) | 104.3(2) | 104.3(2) |
| C(i12)-C(i13) | 1.503(3) | 1.499(4) | N(i10)-C(i11)-C(i07) | 112.5(2) | 112.3(3) |
| C(i04)-C(i05)-C(i06)-C(i07) | 3.3(4) | 0.6(4) | N(i10)-N(i09)-C(i12) | 119.4(2) | 120.0(2) |
| C(i05)-C(i06)-C(i07)-C(i08) | 83.6(4) | -97.2(3) | C(i08)-N(i09)-C(i12) | 128.4(2) | 127.9(3) |
| N(i10)-N(i09)-C(i12)-C(i13) | -83.1(3) | 70.9(3) | N(i09)-C(i12)-C(i13) | 113.0(3) | 113.2(2) |
| N(i09)-C(i12)-C(i13)-C(i14) | -61.9(4) | 74.8(4) | | | |

c) Hydrogen interactions

| C-H···Centroid | C-H | C···Centr. | H···Centr. | C-H···Centr. |
|---|---|---|---|---|
| C(111)-H(111)...C(A)(-x,-y,-z) | 0.97(4) | 3.597(3) | 2.68(3) | 159(3) |
| C(212)-H(2122)...C(B)(x-1,y,z) | 1.03(3) | 3.613(3) | 2.79(3) | 138(2) |
| C(208)-H(208)...C(C)(x-1,y,z) | 0.94(3) | 3.651(3) | 2.78(3) | 155(2) |

Centroid···Centroid

| | |
|---|---|
| C(A)···C(A)(-x,-y-1,-z) | 4.318(2) |
| C(B)-C(D) | 4.407(2) |

| X-H...Y | X-H | X...Y | H...Y | X-H...Y |
|---|---|---|---|---|
| N(201)-H(201)...N(101) | 0.86(2) | 2.897(3) | 2.36(3) | 120(3) |
| N(201)-H(201)...N(101)(1-x,1-y,1-z) | 0.86(2) | 2.919(3) | 2.37(3) | 121(3) |
| C(203)-H(203)...N(110)(-x,-y,-z) | 0.97(2) | 3.480(3) | 2.67(2) | 141(2) |
| C(212)-H(2121)...N(210)(-x-1,-y,1-z) | 1.01(2) | 3.488(3) | 2.51(2) | 166(2) |
| C(217)-H(217)...N(110)(x-1,y,1+z) | 1.02(3) | 3.449(4) | 2.62(3) | 138(2) |

αααα αααβ ααββ αβαβ

The methylene bridge of the benzyl groups in compound **7b** can be used as a stereoisomeric probe in $^1$H NMR spectroscopy. We have summarized in Table 2 the predictions based on symmetry considerations; concerning the chemical shifts, we have taken into account three situations: a group surrounded by two groups in the same orientation, α[αα] ≡ β[ββ], one group surrounded by one group in the same orientation and the other in the opposite orientation, α[αβ] ≡ β[αβ], and one group surrounded by two groups in the opposite orientation, α[ββ] ≡ β[αα].

**Table 2.** $^1$H NMR spectroscopy of methylene signals in porphyrin **7b**

| Atropisomer | Systems | Situation | Chemical shift | Relative intensity |
|---|---|---|---|---|
| αααα | 4 $A_2$ | α[αα] | 5.035 | 1 |
| | 2 AB | α[αβ] | 5.108[a] | 2 |
| ααβ | 1 $A_2$ | α[αα] | 5.049 | 1 |
| | 1 $A_2$ | β[αα] | 5.173 | 1 |
| ααββ | 4 AB | α[αβ] | 5.113[a] | 2 |
| αβαβ | 4 $A_2$ | α[ββ] | 5.173 | 1 |

[a] $J_{AB}$ = 16 Hz ($\Delta\nu_{AB}$ = 0.02 ppm).

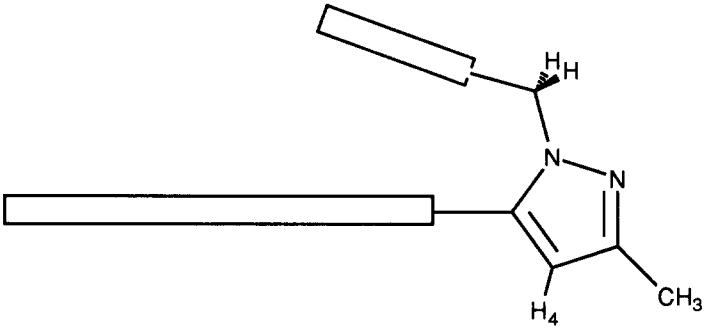
Both the appeareance ($A_2$ vs AB) and the chemical shifts (shielded when surrounding groups are on the same side) agrees with the predictions. The relative intensities correspond, within the precision limits of $^1$H NMR spectroscopy, to the statistical distribution: 12.5 % of αααα (1), 50 % of ααβ (4), 25 % of ααββ(2) and 12.5 % of αβαβ (1). Although the signals of pyrrole protons are too difficult to be assigned and those of the pyrazole methyl groups appeared overlapped (2.686, 2.702, 2.718 ppm in a 1:2:1 ratio, probably corresponding to the α[αα], α[αβ] and α[ββ] situations), a series of selective 1D TOCSY experiments allowed to establish relations between groups due to small scalar couplings between methylene, pyrazole-$H_4$ and phenyl protons (Table 3).

**Table 3.** $^1$H NMR chemical shifts of porphyrin **7b**

| Atropisomer | Methylene | $H_4$ | $H_{ortho}$ | $H_{meta}$ | $H_{para}$ |
|---|---|---|---|---|---|
| αααα | 5.035 | 7.055 | 6.344 | 6.669 | 6.877 |
| | 5.108 | 7.084 | 6.437 | 6.747 | 6.911 |
| ααβ | 5.049 | 7.016 | 6.528 | 6.780 | 6.921 |
| | 5.173 | 6.989 | 6.412 | 6.681 | 6.864 |
| ααββ | 5.113 | 6.952 | 6.444 | 6.665 | 6.844 |
| αβαβ | 5.173 | 6.925 | 6.584 | 6.791 | 6.936 |

It can be seen that two different phenyl groups are correlated with the methylene signal at 5.173 ppm, proving that the isochrony of these signals is accidental (one belongs to the αααβ and the other to the αβαβ atropisomer).

With regard to the $^1H$ NMR spectra of other pyrazoles, the chemical shifts of the *meso*-pyrazolyl substituents in porphyrin **7b** are very different. Compound **18**, 1-benzyl-3-methyl-5-phenylpyrazole) was used as a model, since it is similar to **7b**, the only difference being that the porphyrin central ring has been replaced by a phenyl ring. In **18** the common signals appear at 2.21 (Me), 5.34 ($CH_2$), 6.38 ($H_4$), 7.15 ($H_o$) and 7.25-7.40 ppm ($H_m$ + $H_p$). With regard to porphyrin protons (average values) the following effects are observed: -0.5 (Me), +0.2 ($CH_2$), -0.6 ($H_4$), +0.7 ($H_o$), + 0.5 ppm ($H_m$ + $H_p$). A conformation like that represented below schematically could account for these effects:




## Conclusions

The preparation of 3(5)-formylpyrazoles is easy and reliable; on the other hand, the synthesis of 4-formylpyrazoles has the problem of the Vilsmeier-Haack step. With these two systems of formylpyrazoles comparatively good yields of porphyrins have been obtained. The synthetic pathway which has been developed allows the synthesis of *meso*-substituted porphyrins in a preparative scale of up to 20 mmol of starting material. Finally, the deprotective cleavage of the PMB and SEM groups can be accomplished in rather good yields to obtain the *meso*-tetrakis(N*H*-pyrazolyl)porphyrins. The study of proton transfers in the solid state involving simultaneously the porphyrin central core and the peripheral N*H*-pyrazoles should await the synthesis of $^{15}N$ labelled derivatives.

## Experimental part

*Synthesis*.- Melting points were obtained on a hot stage microscope and are uncorrected. Optical absorption spectra were recorded with a Perkin-Elmer 550-SE UV/VIS spectrophotometer. The concentration of porphyrins used ranged from $10^{-5}$ M (Soret bands) to $10^{-4}$ M (Q bands). IR spectra were recorded with a Perkin-Elmer 681 spectrometer. Mass spectra of the intermediate compounds were determined on a VG2-250 quadrupole mass spectrometer (electron impact)while those of the porphyrins were obtained on a Kratos Concept 32S (electron impact or FAB). Elemental analyses were carried out with a Fisons EA-1108 apparatus. Column chromatography

was performed using silicagel Merck 60 (230-400 mesh) or neutral aluminium oxide (Fluka 100-125 mesh). Preparative layer chromatography was performed using silicagel 60 $PF_{254}$. Pyrrole was distilled on calcium hydride and stored at -17°C over calcium hydride. Dichloromethane was Merck p.a. quality and stored over 4 Å molecular sieves. Imidazole-2-carbaldehyde **12** is a commercial product.

*X-Ray Analysis.*- A summary of data collection and refinement process is given in Table 4. Data were collected at 200 K using an Oxford Cryostream device; the stated temperature was measured continuously during data collection. The structure was solved by direct methods (SIR92)[33] and refined by least-squares procedures on $F_{obs}$. All hydrogen atoms were obtained from difference Fourier synthesis and included and refined isotropically in the last cycles. The scattering factors were taken from the *International Tables for X-Ray Crystallography*.[34] Table 5 lists the final atomic coordinates and equivalent thermal factors for non-hydrogen atoms. The calculations were carried out with the XTAL,[25] PESOS,[35] and PARST[36] set of programs running on a VAX6410 computer.

*NMR Spectroscopy.*- Most spectra were recorded on a Varian Geminy 200 spectrometer. For the particular study of porphyrin **7b** the spectra were determined on a Varian Unity 500 working at 499.84 MHz for proton and 125.70 MHz for carbon 13.

*1,1-Diethoxy-2,4-pentanedione* .[18,19]

A 60 % dispersion of NaH in mineral oil (11.6 g, 0.29 mol) was washed twice with 10 mL dry toluene to remove the mineral oil, then 150 mL toluene and 11.3 mL dry methanol were added, the mixture was cooled to -8 to -10 °C and a mixture of 50 mL (0.28 mol) ethyl diethoxyacetate and 20.5 mL (0.28 mol) acetone was added dropwise during approximately 3 h. The mixture was stirred at a temperature lower than 10 °C for 1 h and left overnight in the refrigerator at 3 °C. Under stirring and cooling the solution was poured into a cooled mixture of 40 mL glacial acetic acid and 40 mL water. The organic layer was separated and the aqueous layer extracted four times with 50 mL ether each time. The combined organic extracts were washed with water, with aqueous $NaHCO_3$ until free of acid and washed again with water. The solution was dried over $Na_2SO_4$, the solvent evaporated and the remaining product distilled under reduced pressure. Yield 31.8 g (60 %), colourless oil, lit.: 70 - 75 %,[18,19] bp 44-48 °C/0.1 torr. $^1H$ NMR ($CDCl_3$) δ 1.25 (t, 6H, O-$CH_2$-$\underline{CH_3}$, $J$ = 7.0 Hz); 2.12 (s, 3H, -CO-$\underline{CH_3}$), 3.5-3.8 (m, 4H, O-$\underline{CH_2}$), 4.81 (s, 1H, $\underline{CH}$), 5.90 (s, 1H, CO-$\underline{CH}$=COH).

*5(3)-Diethoxymethylen-3(5)-methylpyrazole* [**9a**(**10a**)].[18]

1,1-Diethoxy-2,4-pentanedione (21.7 g, 0.115 mol) was added during 2.5 h at 10-15 °C to a solution of 15.0 g (0.115 mol) hydrazine sulfate in 100 mL 10 % aqueous NaOH. After complete addition the solution was stirred for another hour at a temperature lower than 15 °C. The oily layer was separated, 70 mL of water were added to dissolve the precipitated sodium sulfate, the aqueous solution was extracted four times with 50 mL ether each time and the combined organic extracts dried over $K_2CO_3$. The solvent was evaporated and the remaining crude product purified by vacuum distillation. Yield 10.6 g (50 %) colourless oil, lit.: 75 %;[18] bp 95-98 °C/0.1 torr; 94-96 °C/0.001 torr. MS m/z 184 (M). $^1H$ NMR ($CDCl_3$) δ 1.21 (t, 6H, O-$CH_2$-$\underline{CH_3}$, $J$ = 7.0 Hz); 2.28 (s, 3H, pyrazole-$\underline{CH_3}$), 3.45-3.7 (m, 4H, O-$\underline{CH_2}$), 5.58 (s, 1H, $\underline{CH}$), 6.08 (s, 1H, pyrazole-$\underline{H_4}$). Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.39; H, 9.02; N, 15.11.

*1-Benzyl-5-diethoxymethylen-3-methylpyrazole* (**9b**).

1,1-Diethoxy-2,4-pentanedione (13.1 g, 70 mmol) was added slowly (during approximately 2 h) at 10-15 °C to a solution of 13.6 g (70 mmol) benzylhydrazine dihydrochloride in 60 mL 10 % aqueous NaOH. After complete addition the mixture was left for 1 h at room temperature, the oily layer was separated and the aqueous layer was diluted with water to dissolve precipitated salt. The aqueous phase was extracted with ether (4 x 20

Table 4. Crystal analysis parameters at 200K.

*Crystal data*

| | | | |
|---|---|---|---|
| Chemical formula | $C_{60}H_{46}N_{12}$ | Crystal system | Triclinic |
| *Mr* | 935.104 | Space group | *P-1* |
| *a* (Å) | 8.6917(13) | α (°) | 101.130(25) |
| *b* (Å) | 12.3408(33) | β (°) | 105.600(19) |
| *c* (Å) | 12.8711( 34) | γ (°) | 109.280(24) |
| Z | 1 | *Dx* (gr/cm³) | 1.30 |
| V (Å³) | 1193.3(6) | Radiation | CuKα |
| Wavelength (Å) | 1.5418 | No. of reflections for | |
| θ range for lattice parameters (°) | 2-45 | lattice parameters: | 45 |
| Absorption coefficient ($cm^{-1}$) | 5.93 | Temperature (K) | 200 |
| Crystal colour | Deep red | Crystal description | Prism |
| Crystal size (mm) | 0.43 x 0.13 x 0.2 | | |

*Data collection*

| | | | |
|---|---|---|---|
| Diffractometer type | Philips PW1100, four circle. Graphite oriented monocromator. | | |
| Measurement time | 1 min./reflection | Detector apertures (°) | 1 x 1 |
| Collection method | ω/2θ scans | $\theta_{max}$ (°) | 65 |
| No. of standard reflections (interval) | 2 (90 min.). No variation | Scan width (°) | 1.5 |
| No. of independent reflections | 4067 | No. of observed reflections, I>3σ(I) | 3503 |

*Refinement*

| | | | |
|---|---|---|---|
| Treatment of hydrogen atoms | See experimental part | Refinement: Least-Squares on *Fo*. Full matrix | |
| Secondary extinction correction ($10^4$) | 0.25(3) | | |
| *R* | 0.047 | No. of parameters refined | 418 |
| *wR* | 0.057 | Degrees of freedom | 3085 |
| $(\Delta\rho)_{max}$ (e/Å³) | 0.25 | Ratio of freedom | 7.4 |
| <Shift/error> | 0.0003 | Max. thermal value (Å$^2$) | U11[C(115)]=0.082(2) |

Weighting scheme: Empirical as to give no trends in $<\omega\Delta^2F>$ vs. <|Fobs|> and $<\sin\theta/\lambda>$.

Table 5. Final atomic coordinates and $Ueq=(1/3)\Sigma[Uij\cdot a_i^*\cdot a_j^*\cdot a_i\cdot a_j\cdot\cos(a_i,a_j)]\times10^3$

| Atom | x | y | z | Ueq | Atom | x | y | z | Ueq |
|---|---|---|---|---|---|---|---|---|---|
| N(101) | 0.6131(2) | 0.4625(1) | 0.3870(1) | 32(1) | N(201) | 0.2809(2) | 0.3393(2) | 0.4078(1) | 33(1) |
| C(102) | 0.7713(3) | 0.5342(2) | 0.3865(2) | 33(1) | C(202) | 0.2637(3) | 0.2552(2) | 0.3132(2) | 33(1) |
| C(103) | 0.8038(3) | 0.4778(2) | 0.2892(2) | 40(1) | C(203) | 0.1041(3) | 0.1545(2) | 0.2846(2) | 41(1) |
| C(104) | 0.6645(3) | 0.3731(2) | 0.2317(2) | 39(1) | C(204) | 0.0306(3) | 0.1784(2) | 0.3622(2) | 43(1) |
| C(105) | 0.5452(3) | 0.3637(2) | 0.2928(2) | 32(1) | C(205) | 0.1413(3) | 0.2950(2) | 0.4410(2) | 35(1) |
| C(106) | 0.3846(3) | 0.2655(2) | 0.2586(2) | 32(1) | C(206) | 0.1150(3) | 0.3525(2) | 0.5355(2) | 34(1) |
| C(107) | 0.3356(3) | 0.1618(2) | 0.1577(2) | 34(1) | C(207) | –0.0455(3) | 0.2818(2) | 0.5539(2) | 34(1) |
| C(108) | 0.3828(3) | 0.0660(2) | 0.1536(2) | 42(1) | C(208) | –0.2049(3) | 0.2887(2) | 0.5225(2) | 39(1) |
| N(109) | 0.3072(2) | –0.0076(1) | 0.0455(1) | 38(1) | N(209) | –0.3139(2) | 0.2024(2) | 0.5498(1) | 36(1) |
| N(110) | 0.2113(2) | 0.0346(2) | –0.0223(1) | 41(1) | N(210) | –0.2347(2) | 0.1381(2) | 0.5980(2) | 40(1) |
| C(111) | 0.2292(3) | 0.1372(2) | 0.0461(2) | 41(1) | C(211) | –0.0721(3) | 0.1867(2) | 0.6003(2) | 40(1) |
| C(112) | 0.3056(3) | –0.1263(2) | 0.0001(2) | 47(1) | C(212) | –0.5009(3) | 0.1694(2) | 0.5266(2) | 43(1) |
| C(113) | 0.1524(3) | –0.2283(2) | 0.0008(2) | 41(1) | C(213) | –0.5424(3) | 0.1970(2) | 0.6318(2) | 39(1) |
| C(114) | 0.1305(4) | –0.2375(2) | 0.1024(2) | 52(1) | C(214) | –0.5056(3) | 0.3145(2) | 0.6895(2) | 51(1) |
| C(115) | –0.0117(4) | –0.3306(2) | 0.1022(3) | 62(1) | C(215) | –0.5472(4) | 0.3400(3) | 0.7855(2) | 61(1) |
| C(116) | –0.1305(4) | –0.4159(3) | 0.0028(3) | 64(1) | C(216) | –0.6252(3) | 0.2481(3) | 0.8245(2) | 58(1) |
| C(117) | –0.1094(4) | –0.4080(2) | –0.0991(2) | 60(1) | C(217) | –0.6642(3) | 0.1302(3) | 0.7670(2) | 54(1) |
| C(118) | 0.0314(3) | –0.3143(2) | –0.0992(2) | 46(1) | C(218) | –0.6227(3) | 0.1051(2) | 0.6709(2) | 46(1) |

mL), the combined extracts were washed with saturated NaCl solution, dried with $K_2CO_3$ and the solvent was evaporated. The remaining yellow oil was distilled under reduced pressure using a Kugelrohr apparatus. Yield 10.9 g (57 %), bp 120-140 °C (oven temperature)/0.1 torr. $^1$H NMR ($CDCl_3$) δ 1.11 (t, 6 H, $OCH_2\underline{CH_3}$, $J$ = 7.0 Hz), 2.26 (s, 3 H, pyrazole-$\underline{CH_3}$), 3.47 (m, 4 H, $O\underline{CH_2}CH_3$, $J$ = 7.1 Hz), 5.34 (s, 2 H, $N$-$\underline{CH_2}$), 5.36 (s, 1 H, $\underline{CH}$), 6.14 (s, 1H, pyrazole-$\underline{H_4}$), 7.10-7.27 (m, 5H, phenyl). $^{13}$C NMR ($CDCl_3$) δ 13.44 (pyrazole-$\underline{CH_3}$), 14.81 ($OCH_2\underline{CH_3}$), 53.20 (ar-$\underline{CH_2}$), 61.03 ($O\underline{CH_2}CH_3$), 95.40 ($\underline{CH}$), 105.87 (pyrazole-$\underline{C_4}$), 126.77 (ar-$\underline{CH}$), 127.19 (ar-$\underline{CH}$), 128.34 (ar-$\underline{CH}$), 137.43 (ar-$\underline{C}$), 140.60 (pyrazole-$\underline{C_5}$), 147.21 (pyrazole-$\underline{C_3}$). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.20; H, 7.94; N, 10.12.

*1-[2-(Trimethylsilyl)ethoxy]methyl-5(3)-diethoxymethylen-3(5)-methylpyrazole* (**9c+10c**).

Prepared according to the general procedure described in ref. 16. Under argon, 0.4 g of NaH (60% suspension in mineral oil, 10 mmol) were suspended in 10 mL of dry THF. Then pyrazole [**9a(10a)**] (1.84 g, 10 mmol) in 5 mL of dry THF was added and the mixture stirred for 1 h. After cooling at 0°C, a solution of [2-(trimethylsilyl)ethoxy]methyl chloride (1.77 mL, 10 mmol) in 2 mL of dry THF was added *via* syringe. The cooling bath was removed and the mixture stirred at room temperature for 1.5 h. After addition of water (50 mL) the organic layer was separated, the aqueous phase was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers dried over $Na_2SO_4$. The solvents were evaporated under vacuum. Yield 2.7 g (85%) of a mixture of isomers: 36 % of **9c**, 64 % of **10c** (from $^1$H NMR). MS m/z 314 (M). $^1$H NMR ($CDCl_3$) δ: isomer **9c**: -0.06 [s, 9H, $Si(\underline{CH_3})_3$], 0.85 (m, 2H, $\underline{CH_2}$-Si), 1.22 (t, 6H, O-$CH_2$-$\underline{CH_3}$, $J$ = 7.2 Hz), 2.21 (s, 3H, pyrazole-$\underline{CH_3}$), 3.46-3.69 (m, 6H, O-$\underline{CH_2}$-$CH_3$ and O-$\underline{CH_2}$-$CH_2$), 5.41 (s, 2H, $N$-$\underline{CH_2}$-O),5.67 (s, 1H, $\underline{CH}$), 6.16 (s, 1H, pyrazole-$\underline{H_4}$); isomer **10c**: -0.07 [s, 9H, $Si(\underline{CH_3})_3$], 0.85 (m, 2H, $\underline{CH_2}$-Si), 1.25 (t, 6H, O-$CH_2$-$\underline{CH_3}$, $J$ = 7.2 Hz), 2.31 (s, 3H, pyrazole-$\underline{CH_3}$), 3.46-3.69 (m, 6H, O-$\underline{CH_2}$-$CH_3$ and O-$\underline{CH_2}$-$CH_2$), 5.35 (s, 2H, $N$-$\underline{CH_2}$-O), 5.46 (s, 1H, $\underline{CH}$), 6.15 (s, 1H, pyrazole-$\underline{H_4}$). Anal. Calcd for $C_{15}H_{30}N_2O_3Si$: C, 57.28; H, 9.60; N, 8.90. Found: C, 57.11; H, 9.71; N, 8.86.

*1-p-Methoxybenzyl-5(3)-diethoxymethylen-3(5)-methylpyrazole* (**9d+10d**).

Prepared according to the general procedure described in ref. 37 (solvent not reported). 5(3)-Diethoxymethylen-3(5)-methyl-pyrazole [(**9a(10a)**] (8.0 g, 43 mmol) 4.7 g $K_2CO_3$, 1.9 g finely powdered KOH, 0.2 g tetrabutylammonium bromide (TBAB) and 6.7 g (43 mmol) *p*-methoxybenzyl chloride in 300 mL dry toluene were heated at reflux for 20 h. The mixture was filtered, the precipitate was washed several times with toluene, and the combined organic solutions were evaporated to dryness. The remaining oil was distilled under reduced pressure. Yield 7.75 g (59 %) colourless oil, approx. 1/1 mixture of both possible isomers bp 150-165 °C. $^1$H NMR ($CDCl_3$) δ 2.21 (s, 3H, 3-$\underline{CH_3}$ of **9d**), 2.29 (s, 3 H, 5-$\underline{CH_3}$ of **10d**), 3.74, 3.76 (2 s, 3 H, $O\underline{CH_3}$), 5.27, 5.56 (2 s, 2 H, $N$-$\underline{CH_2}$), 6.55, 6.64 (2 s, 1 H, pyrazole-$\underline{H_4}$), 6.77-6.86 (m, 2H, ar-$\underline{H}$), 7.05-7.24 (m, 2 H, ar-$\underline{H}$). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.94; N, 9.20. Found: C, 66.91; H, 8.02; N, 9.09.

*5(3)-Formyl-3(5)-methylpyrazole* [(**5a(6a)**].[19]

In the solid state this compound exists as a dimer (4,5-dihydroxy-2,7-dimethyl-4*H*,9*H*-dipyrazolo[2,3-*a*:2',3'-*d*]pyrazine) which was characterized by IR spectroscopy and mass spectrometry. In solution, the free aldehyde monomer predominates. 5(3)-Diethoxymethylene-3(5)-methylpyrazole [(**9a(10a)**] (2.50 g, 13.6 mmol) was dissolved in 20 mL 1 % hydrochloric acid. The mixture was left at room temperature for 10 h, the precipitate was filtrated, washed with methanol and water and dried under vacuum. Yield 1.44 g (96 %) colourless powder; Lit.: 94 %;[11] mp 180 °C (dec);[11] mp 188-189 °C (dec). $^1$H NMR ($CDCl_3$+ a drop of $CF_3CO_2H$) δ 2.56 (s, 3H, $\underline{CH_3}$), 6.86 (s, 1H, pyrazole-$\underline{H_4}$), 10.02 (s, 1 H, $\underline{CHO}$). IR (KBr) 3120 $cm^{-1}$ ($\nu_{OH}$). MS m/z 220 (M). $^{13}$C

NMR ($CDCl_3$+ a drop of $CF_3CO_2H$) δ 11.26 ($\underline{C}H_3$), 107.49 (pyrazole-$\underline{C}_4$), 144.68 ($\underline{C}$-$CH_3$),146.29 ($\underline{C}$-CHO), 182.77 ($\underline{C}$HO). Anal. Calcd for $C_5H_6N_2O$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.31; H, 5.74; N, 25.16.

*1-Benzyl-5-formyl-3-methylpyrazole* (**5b**).

Pyrazole **9b** (3.50 g, 12.8 mmol) was dissolved in 20 mL 1 % HCl and 3 mL ethanol were added to improve miscibility. The mixture was stirred at room temperature for 30 h, neutralized with saturated $NaHCO_3$ solution and extracted with ether (4 x 15 mL). The combined organic extracts were dried with $Na_2SO_4$, then the solvent was evaporated. The crude product was sufficiently pure to be used for the following step. Yield: 2.51 g (98 %) colourless oil. $^1H$ NMR ($CDCl_3$) δ 2.30 (s, 3 H, 3-$\underline{CH}_3$), 5.63 (s, 2 H, *N*-$\underline{CH}_2$), 6.60 (s, 1 H, pyrazole-$\underline{H}_4$), 7.20-7.29 (m, 5 H, ar-$\underline{H}$), 9.74 (s, 1 H, $\underline{CHO}$). $^{13}C$ NMR ($CDCl_3$) δ 13.23 (pyrazole-$\underline{C}H_3$), 54.52 (*N*-$\underline{C}H_2$), 114.60 (pyrazole-$\underline{C}_4$), 127.45 (ar-$\underline{C}$), 127.65 (ar-$\underline{C}$), 128.41 (ar-$\underline{C}$), 136.66 (ar-$\underline{C}$), 139.09 (pyrazole-$\underline{C}_5$), 148.34 (pyrazole-$\underline{C}_3$), 179.53 ($\underline{C}$HO). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.09; H, 5.93; N, 13.86.

*1-[2-(Trimethylsilyl)ethoxy]methyl-5(3)-formyl-3(5)-methylpyrazole* (**5c+6c**).

The mixture of pyrazoles (**9c+10c**) (1.87 g, 5.9 mmol) was dissolved in a 30 mL solution of 1% HCl and the work-up was similar to that used for **5a**(**6a**). The aqueous phase was extracted with ethyl acetate (3 x 20 mL), washed with $NaHCO_3$ solution and then with water. The organic extract was dried with $Na_2SO_4$, the solvent was evaporated under vacuum affording the crude mixture of **5c+6c**, 1.3 g (91%), bp 138 °C (oven temperature)/0.3 torr. According to $^1H$ NMR it is a mixture of 33% of **5c** and 67 % of **6c**. IR (neat) 1700 $cm^{-1}$ ($\nu_{C=O}$). MS m/z 241 (M+1). Anal. Calcd for $C_{11}H_{20}N_2O_2Si$: C, 54.96; H, 8.38; N, 11.65. Found: C, 55.10; H, 8.60; N, 11.91. $^1H$ NMR ($CDCl_3$) δ isomer **5c**: -0.04 [s, 9 H, Si($\underline{CH}_3$)$_3$], 0.89 (m, 2 H, $\underline{CH}_2$-Si), 2.33 (s, 3 H, pyrazole-3-$\underline{CH}_3$), 3.57 (m, 2 H, O$\underline{CH}_2$C), 5.73 (s, 2 H, *N*-$\underline{CH}_2$), 6.73 (s, 1 H, pyrazole-$\underline{H}_4$), 9.87 (s, 1 H, $\underline{CHO}$); isomer **6c**: -0.03 [s, 9 H, Si($\underline{CH}_3$)$_3$], 0.89 (m, 2 H, $\underline{CH}_2$-Si), 2.39 (d, 3 H, pyrazole-5-$\underline{CH}_3$, $J$ = 0.8 Hz), 3.57 (m, 2 H, O$\underline{CH}_2$C), 5.47 (s, 2 H, *N*-$\underline{CH}_2$), 6.58 (s, 1 H, pyrazole-$\underline{H}_4$), 9.92 (s, 1 H, $\underline{CHO}$); $^{13}C$ NMR ($CDCl_3$) δ isomer **5c**: -1.56 [Si($\underline{C}H_3$)$_3$], 13.21 (pyrazole-3-$\underline{C}H_3$), 17.56 ($\underline{C}H_2$Si), 66.52 (O$\underline{C}H_2$C), 78.62 (*N*-$\underline{C}H_2$), 114.73 (pyrazole-$\underline{C}_4$), 139.60 (pyrazole-$\underline{C}_5$), 148.8 (pyrazole-$\underline{C}_3$), 179.51 ($\underline{C}$HO); isomer **6c**: -1.56 [Si($\underline{C}H_3$)$_3$], 10.76 (pyrazole-5-$\underline{C}H_3$), 17.56 ($\underline{C}H_2$Si), 66.58 (O$\underline{C}H_2$C), 78.62 (*N*-$\underline{C}H_2$), 105.75 (pyrazole-$\underline{C}_4$), 141.43 (pyrazole-$\underline{C}_5$), 148.80 (pyrazole-$\underline{C}_3$), 186.69 ($\underline{C}$HO).

*1-p-Methoxybenzyl-3(5)-methyl-5(3)-formylpyrazole* (**5d+6d**).

The mixture of pyrazoles **9d+10d** (3.65 g, 12 mmol) was dissolved in a 20 mL solution of 1 % HCl, 2 mL ethanol were added to increase miscibility. The mixture was stirred at room temperature for 10 h, neutralized with saturated $NaHCO_3$ solution and extracted with ether (4 x 15 mL). The combined organic extracts were dried with $Na_2SO_4$, the solvent evaporated and the crude product was distilled with a Kugelrohr apparatus. Yield 2.60 g (94 %) colourless oil; bp 130-140 °C (oven temperature)/0.05 torr. $^1H$ NMR ($CDCl_3$) δ isomer **5d**: 2.21 (s, 3 H, 3-$\underline{CH}_3$), 3.74 (s, 3 H, O$\underline{CH}_3$), 5.56 (s, 2 H, *N*-$\underline{CH}_2$), 6.64 (s, 1 H, pyrazole-$\underline{H}_4$), 6.80 (m, 2 H, ar-$\underline{H}$, $J$ = 8.6 Hz), 7.07 (m, 2 H, ar-$\underline{H}$, $J$ = 8.6 Hz), 9.74 (s, 1 H, $\underline{CHO}$); isomer **6d**: 2.29 (s, 3 H, 5-$\underline{CH}_3$), 3.76 (s, 3 H, O$\underline{CH}_3$), 5.27 (s, 2 H, *N*-$\underline{CH}_2$), 6.55 (s, 1 H, $\underline{H}_4$), 6.77 (m, 2 H, ar-$\underline{H}$, $J$ = 8.4 Hz), 7.24 (m, 2 H, ar-$\underline{H}$, $J$ = 8.4 Hz), 9.91 ($\underline{CHO}$). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 68.01; H, 6.02; N, 12.15.

*1-(tert-Butyloxycarbonyl)-3-formyl-5-methylpyrazole* (**6e**).

Prepared following a procedure similar to that described in ref. 17. 4-Dimethylaminopyridine (DMAP) 122 mg (1 mmol) and di-*tert*-butyldicarbonate 2.62 g (12 mmol) were added to a stirred suspension of pyrazole

**5a**(**6a**) 1.1 g (10 mmol) in dry acetonitrile (20 mL) at room temperature. After 1h, a clear solution was obtained which was left at room temperature overnight. The solution was partitioned between diethyl ether (100 mL) and 1M $KHSO_4$ aqueous solution (50 mL), the ether phase was washed with 25 mL portions of 1M $KHSO_4$ (5 times), water (1 time), 1M $NaHCO_3$ and brine (3 times) and subsequent drying ($MgSO_4$). The crude was purified by column chromatography on silica gel using a dichloromethane gradient with ethyl acetate. In this way 0.068 g (3%) of **5e** was obtained. IR (neat) 1705, 1760 $cm^{-1}$ ($\nu_{CHO}$ and $\nu_{COO}$). MS m/z 210 (M). $^1H$ NMR ($CDCl_3$) δ 1.68 [s, 9 H, C($\underline{CH_3}$)$_3$], 2.58 (d, 3 H, $\underline{CH_3}$, $J$ = 0.9 Hz), 6.58 (s, 1 H, pyrazole-$\underline{H_4}$), 10.01 (s, 1 H, $\underline{CHO}$). $^{13}C$ NMR ($CDCl_3$) δ 14.59 (pyrazole-5-$\underline{C}H_3$), 27.79 [(C($\underline{C}H_3$)$_3$], 86.69 [($\underline{C}$(CH$_3$)$_3$], 107.38 (pyrazole-$\underline{C_4}$), 145.21 (pyrazole-$\underline{C_5}$), 146.06 (pyrazole-$\underline{C_3}$), 163.71 ($\underline{CO_2}$), 186.69 ($\underline{C}$HO).Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.21; H, 6.74; N, 13.16.

*1-Benzylpyrazole* (**11a**).

This known compound was prepared in two ways: by reaction of benzylhydrazine with tetramethoxypropane and by benzylation of pyrazole according to ref. 37.

*1*-p-*Methoxybenzylpyrazole* (**11b**).

Tetramethoxypropane (5.0 mL, 30 mmol) and 4.56 g (30 mmol) *p*-methoxybenzylhydrazine in 20 mL ethanol and 20 mL 0.8 N HCl were heated at reflux for 1 h. The solvent was evaporated, the residue washed with dilute aqueous sodium hydroxide solution and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried with $K_2CO_3$ and the solvent evaporated. The crude product was purified by distillation under reduced pressure using a Kugelrohr apparatus. Yield 3.62 g (64 %); bp 100 °C (oven temperature)/0.05 torr. $^1H$ NMR ($CDCl_3$) δ 3.77 (s, 3 H, O$\underline{CH_3}$), 5.23 (s, 2 H, *N*-$\underline{CH_2}$), 6.24 (t, 1 H, pyrazole-$\underline{H_4}$), 6.85 (dd, 2 H, ar-$\underline{H}$, *o*-OCH$_3$ , $J$ = 6.6, $J$ = 2.1 Hz), 7.16 (dd, 2 H, ar-$\underline{H}$, *m*-OCH$_3$ , $J$ = 6.5, $J$ = 2.1 Hz), 7.32 (d, 1 H, pyrazole-$\underline{H_5}$, $J$ = 1.9), 7.52 (d, 1 H, pyrazole-$\underline{H_3}$, $J$ = 2.1). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.42; N, 14.88. Found: C, 70.22; H, 6.37; N, 14.96.

*1*-p-*Methoxybenzyl-3,5-dimethylpyrazole* (**11c**).

2,4-Pentanedione (3.55 mL, 34.8 mmol) and 5.29 g (34.8 mmol) *p*-methoxybenzylhydrazine in 20 mL ethanol and 20 mL 0.8 N HCl were heated at reflux for 1 h. The solvent was evaporated, the residue washed with dilute aqueous sodium hydroxide solution and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried with $K_2CO_3$ and the solvent evaporated. The crude product can be purified by distillation under reduced pressure using a Kugelrohr apparatus although it is sufficiently pure to be used in the following step. Yield 4.76 g (73 %), bp 100 °C (oven temperature)/0.05 torr. $^1H$ NMR ($CDCl_3$) δ 2.15 (s, 3 H, $\underline{CH_3}$), 2.24 (s, 3 H, $\underline{CH_3}$), 3.78 (s, 3 H, O$\underline{CH_3}$), 5.15 (s, 2 H, *N*-$\underline{CH_2}$), 5.83 (s, 1 H, pyrazole-$\underline{H_4}$), 6.83 (dd, 2 H, ar-$\underline{H}$, *o*-OCH$_3$ , $J$ = 6.7, $J$ = 2.1 Hz), 7.04 (dd, 2 H, ar-$\underline{H}$, *m*-OCH$_3$ , $J$ = 6.7, $J$ = 2 Hz). $^{13}C$ NMR ($CDCl_3$) δ 11.15 (5-$\underline{C}H_3$), 13.53 (3-$\underline{C}H_3$), 52.16 (*N*-$\underline{C}H_2$), 55.25 (O$\underline{C}H_3$), 114.05 (ar-$\underline{C}$), 128.00 (ar-$\underline{C}$). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.45; N, 12.95. Found: C, 72.23; H, 7.48; N, 12.76.

*1-Benzyl-4-formylpyrazole* (**3a**).

Following a procedure similar to that described in ref. 38. Under stirring and exclusion of moisture 17.13 mL (222 mmol) DMF were added to 20.14 mL ( 220 mmol) $POCl_3$ at 1-10 °C (both freshly distilled). After complete addition the mixture was stirred for 1 h at room temperature. It was then heated up to 80 °C and 15.8 g (0.1 mol) of pyrazole **11a** was added dropwise. The temperature was then increased to *ca.* 80-85 °C (1 h), 95-100°C (3 h) and 110- 115 °C (1 h) . The still hot mixture was poured into approx. 250 mL of ice, the flask being cooled in an ice bath. The reaction mixture was diluted with more water (100 mL) and left at room temperature

overnight to complete the hydrolysis. Saturated $NaHCO_3$ solution was added (p*H* approx. 5-6) and the solution extracted with dichloromethane (4 x 100 mL). The combined organic extracts were washed with a saturated NaCl solution and dried with $Na_2SO_4$. The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography (silica gel, cyclohexane/ethyl acetate 9:1, gradient ethyl acetate). Yield 10.9 g (59 %). IR (KBr) 1665 ($\nu_{CHO}$). MS m/z 186 (M). $^1$H NMR ($CDCl_3$) δ 5.33 (s, 2 H, *N*-$\underline{CH_2}$), 7.25-7.40 (m, 5H, phenyl), 7.88 (s, 1 H, pyrazole-$\underline{H_5}$), 7.99 (s, 1 H, pyrazole-$\underline{H_3}$), 9.82 (s, 1 H, $\underline{CHO}$). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.13; H, 5.72; N, 15.26.

*1*-p-*Methoxybenzyl-4-formylpyrazole* (**3b**).

Similarly to compound **3a** but starting from pyrazole **11b** (3.5 g, 18.6 mmol). The final dark brown viscous oil was purified by vacuum distillation using a Kugelrohr apparatus. Yield 0.91 g (24 %) viscous yellow oil; bp 150 °C (oven temperature)/0.05 torr. $^1$H NMR ($CDCl_3$) δ 3.79 (s, 3 H, O$\underline{CH_3}$), 5.25 (s, 2 H, *N*-$\underline{CH_2}$), 6.90 (dd, 2 H, ar-$\underline{H}$, *o*-$OCH_3$ , $J$ = 6.4, $J$ = 2.3 Hz), 7.2 (dd, 2 H, ar-$\underline{H}$, *m*-$OCH_3$ , $J$ = 6.8, $J$ = 2.3 Hz), 7.81 (s, 1 H, pyrazole-$\underline{H_5}$), 7.97 (s, 1 H, pyrazole-$\underline{H_3}$), 9.80 (s, 1 H, $\underline{CHO}$). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.49; H, 5.61; N, 12.71.

*1*-p-*Methoxybenzyl-3,5-dimethyl-4-formylpyrazole* (**3c**).

Dimethylformamide (3.8 mL, 48.3 mmol), 4.4 mL (47.9 mmol) $POCl_3$ and 4.7 g (21.8 mmol) pyrazole **11c** were reacted in the same way as for the preceding product. The crude product, a dark brown viscous oil, was purified by vacuum distillation using a Kugelrohr apparatus. Yield 1.63 g (32 %); bp *ca.* 150 °C (oven temperature)/0.05 torr. $^1$H NMR ($CDCl_3$) δ 2.48 (s, 3 H, $\underline{CH_3}$), 2.49 (s, 3 H, $\underline{CH_3}$), 3.81 (s, 3 H, O$\underline{CH_3}$), 5.19 (s, 2 H, *N*-$\underline{CH_2}$), 6.87 (dd, 2 H, ar-$\underline{H}$, *o*-$OCH_3$ , 7.2 (dd, 2 H, ar-$\underline{H}$, *m*-$OCH_3$ ), 7.81 (s, 1 H, pyrazole-$\underline{H_4}$), 9.92 (s, 1 H, $\underline{CHO}$). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 68.90; H, 6.59; N, 11.38.

*1*-p-*Methoxybenzyl-2-formylimidazole* (**13**).

Following the general procedure to alkylate imidazoles described in ref. 39. 2-Formylimidazole (**12**, 0.48 g, 5 mmol), fine powdered $K_2CO_3$ (1.38 g, 10 mmol) and tetrabutylammonium bromide (TBAB) catalyst (0.032 g, 0.1 mmol) were mixed and submerged in an ultrasonic cleaning bath (70 W, 47 kHz) for 15 minutes. *p*-Methoxybenzyl chloride (0.67 mL, 5 mmol) was added at 0 °C and the reaction mixture was stirred at 120 °C for 2 h. The crude mixture was extracted with dichloromethane (2 x 15 mL). Removal of solvent followed by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1) affords pure **13**, 0.365 g (34%). IR (neat) 1690 $cm^{-1}$ ($\nu_{C=O}$). MS m/z 216 (M). $^1$H NMR ($CDCl_3$) δ 3.79 (s, 3H, O$\underline{CH_3}$), 5.53 (s, 2H, *N*-$\underline{CH_2}$), 6.87 (d, 2H, ar-$\underline{H}$, *o*-$OCH_3$, $J$ = 8.8 Hz), 7.10 (t, 1H, imidazole-$\underline{H_5}$, $J$ = 1.0), 7.18 (d, 2H, ar-$\underline{H}$, *m*-$OCH_3$, $J$ = 8.8), 7.27 (d, 1H, imidazole-$\underline{H_4}$, $J$ = 1.0), 9.85 (s, 1H, $\underline{CHO}$). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.21; H, 5.64; N, 12.76.

*1*-(p-*Methoxybenzyl)-2-methylbenzimidazole* (**14**).

A flask with 4.88 g (36.9 mmol) 2-methylbenzimidazole, 4.56 g (40.6 mmol) fine powdered potassium *tert*-butylate and 0.24 g (0.74 mmol, 2 mol%) TBAB was left for 1 h in an ultrasonic bath.[37] The mixture was then cooled in an ice bath, 5 mL (36.9 mmol) *p*-methoxybenzyl chloride were added and the mixture stirred at room temperature for approx. 3 h. It was then extracted with dichloromethane (4 x 25 mL). Evaporation of the solvent and recrystallization from ether/ethanol. Yield 3.75 g (40 %). $^1$H NMR ($CDCl_3$) δ 2.55 (s, 3 H, $\underline{CH_3}$), 3.75 (s, 3 H, O$\underline{CH_3}$), 5.24 (s, 2 H, *N*-$CH_2$), 6.81 (dd, 2 H, ar-$\underline{H}$, *o*-$OCH_3$ , $J$ = 6.6, $J$ = 2.3 Hz), 6.99 (dd, 2

H, ar-H, *m*-$OCH_3$, $J$ = 6.5, $J$ = 2.3 Hz), 7.19-7.25 (m, 3 H, ar-H), 7.68-7.72 (m, 1 H, ar-H). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.99; H, 6.34; N, 11.31.

*1-(p-Methoxybenzyl)-2-formylbenzimidazole* (**15**).

Selenium dioxide (2.3 g, 20.8 mmol = 1.5 molar equivalents) was added to a solution of 3.5 g (13.9 mmol) benzimidazole **14** in 60 mL 1,4-dioxane and heated 3 h at reflux. The mixture was filtered while hot, the precipitate was washed twice with hot dioxane and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (150 g silica gel, cyclohexane/ether 1:1). Yield 2.28 g (62 %). $^1H$ NMR ($CDCl_3$) δ 3.73 (s, 3 H, $OCH_3$), 5.77 (s, 2 H, *N*-$CH_2$), 6.79 (dd, 2 H, ar-H, *o*-$OCH_3$, $J$ = 6.6, $J$ = 2.2 Hz), 7.18 (dd, 2 H, ar-H, *m*-$OCH_3$, $J$ = 6.6, $J$ = 2.2 Hz), 7.34-7.49 (m, 3 H, arene-H), 7.92 (m, 1 H, arene-H), 10.12 (s, 1 H, CHO). $^{13}C$ NMR ($CDCl_3$) δ 47.41 (*N*-$CH_2$), 55,14 ($OCH_3$), 111.33 (s, benzimidazole-$C_2$), 114.09 (ar-C), 122.36 (ar-C), 123.75 (ar-C), 124.09 (ar-C), 126.94 (ar-C), 128.06 (ar-C), 128.41 (ar-C), 136.40 (ar-C), 142.86 (ar-C), 184.86 (CHO). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.29; N, 10.52. Found: C, 72.44; H, 5.11; N, 10.55.

*1-Benzyl-3(or 5)-methyl-5(or 3)-phenylpyrazoles* (**18, 19**).

Benzyl hydrazine hydrochloride (1.95 g, 10 mmol) was added to 8 mL 10 % aqueous NaOH solution and cooled to 15 °C. 1.62 g (10 mmol) 1-phenyl-1,3-butanedione dissolved in 5 mL ethanol were added slowly at this temperature and the solution was stirred 1 h at 15 °C. Water was added to resolve the precipitate and the mixture extracted with ether (4 x 10 mL). The combined ether extracts were washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was recrystallized from ethanol/water. Yield 1.08 g (44 %) mixture of isomers. *ca.* 250 mg of this product was separated by flash chromatography on *ca.* 40 g silica gel with cyclohexane /ethyl acetate 5:1 as eluent.

*1-Benzyl-3-methyl-5-phenylpyrazole* (**18**).

$R_f$ ($SiO_2$, cyclohexane/ethyl acetate 2:1) = 0.40. $^1H$ NMR ($CDCl_3$)[40] δ 2.34 (s, 3 H, $CH_3$), 5.28 (s, 2 H, *N*-$CH_2$), 6.15 (s, 1 H, pyrazole-$H_4$), 7.04 (m, 2 H, ar-$H_o$), 7.25-7.35 (m, 8 H, ar-H). $^{13}C$ NMR ($CDCl_3$) δ 14.16 ($CH_3$), 53.31 (*N*-$CH_2$), 106.58 (pyrazole $C_4$), 127.12 (ar-$C_o$), 127.82 (ar-$C_p$), 128.93 (ar-$C_p$), 129.09 (ar-$C_m$), 129.26 (ar-$C_m$), 131.41 (ar-$C_i$), 138.47 (ar-$C_i$), 145.43 (pyrazole-$C_5$), 148.82 (pyrazole-$C_3$). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.12; H, 6.33; N, 11.31.

*1-Benzyl-3-phenyl-5-methylpyrazole* (**19**).

$R_f$ ($SiO_2$, cyclohexane/ethyl acetate 2:1) = 0.49. $^1H$ NMR ($CDCl_3$)[40] δ 2.21 (s, 3 H, $CH_3$), 5.34 (s, 2 H, *N*-$CH_2$), 6.38 (s, 1 H, pyrazole-$H_4$), 7.15 (m, 2 H, ar-$H_o$), 7.25-7.40 (m, 6 H, ar-H), 7.83 (m, 2 H, 3-phenyl, ar-$H_o$). $^{13}C$ NMR ($CDCl_3$) δ 11.21 ($CH_3$), 53.05 (*N*-$CH_2$), 103.17 (pyrazole-$C_4$), 125.44 (ar-$C_o$), 126.55 (ar-$C_o$), 127.33 (ar-$C_p$), 127.43 (ar-$C_p$), 128.46 (ar-$C_m$), 128.61 (ar-$C_m$), 133.67 (ar-$C_i$), 137.00 (ar-$C_i$), 139.78 (pyrazole-$C_5$), 150.24 (pyrazole-$C_3$). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.39; H, 6.45; N, 11.17.

*General procedure for the synthesis of* meso-*substituted porphyrins*.

We have followed the procedure described in refs. 21 and 41. A 2 litres three-necked round-bottomed flask fitted with a reflux condenser and a nitrogen inlet port was filled with 1 L pure dry dichloromethane and 7.5 mL (0.75 %) dry methanol. Samples of the corresponding aldehyde (10 mmol) and pyrrole (10 mmol) were added. After the solution was purged with nitrogen for about 5 min, a 2.5 M solution of boron trifluoride etherate (3.3 mmol) was added *via* syringe and the reaction vessel was shielded from light. After 1-2 h stirring at room temperature, *p*-chloranil (7.5 mmol, *i.e.* 3 equivalents *per* porphyrinogen) was added in powder form and the

reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, 1 equivalent of triethylamine (3.3 mmol) was added and the solvent evaporated to 50 mL, then 20 g neutral alumina were added and the solution evaporated to dryness. The residue was chromatographed either on alumina or on silica gel or on both successively.

Meso-*Tetrakis-(1-benzylpyrazol-4-yl)porphyrin* (**4a**)

The reaction was performed in 600 mL mixture of dichloromethane and methanol (4.5 mL) containing *N*-benzyl-4-formylpyrazole **3a** (1.116 g, 6 mmol) and pyrrole (0.415 mL, 6 mmol) using 2.5 M $BF_3.OEt_2$ (0.79 mL, 1.98 mmol) followed by oxidation with *p*-chloranil (1.1 g, 4.5 mmol) at reflux (1 h). Triethylamine (0.275 mL, 1.98 mmol) was added to neutralize the acid in excess. Column chromatography (silica gel, dichloromethane/ethyl acetate 9:1, followed by cyclohexane/ethyl acetate 1:1 and ethyl acetate gradient) afforded 0.42 g (8 %) of pure **4a** ($R_f$, $SiO_2$, cyclohexane/ethyl acetate 1:1 = 0.274). MS m/z 934 (M). UV ($CH_2Cl_2$) $\lambda_{max}$ nm (log ε) 422 (5.28), 490 (3.58), 522 (3.92), 564 (3.96), 596 (3.50), 660 (3.56). $^1H$ NMR ($CDCl_3$) δ -2.70 (s, 2 H, NH), 5.70 (s, 8 H, *N*-$CH_2$), 7.40-7.55 (m, 20 H, phenyl), 8.17 (s, 4 H, pyrazole-$H_5$), 8.38 (s, 4 H, pyrazole-$H_3$), 9.05 (s, 8 H, pyrrole-$H_\beta$). Anal. Calcd for $C_{60}H_{46}N_{12}$: C, 77.06; H, 4.95; N, 17.97. Found: C, 76.79; H, 4.73; N, 17.69.

Meso-*Tetrakis-(1-*p*-methoxybenzylpyrazol-4-yl)porphyrin* (**4b**)

The reaction was performed in 440 mL of dichloromethane and methanol (2.2 mL), containing pyrazole **3b** (0.91 g, 4.4 mmol), pyrrole (0.30 mL, 4.4 mmol) and 2.5 M $BF_3.OEt_2$ (0.6 mL, 1.5 mmol), after stirring 1 h at reflux, *p*-chloranil (1.19 g, 4.84 mmol) was added and the reflux continued for 1.5 h. Column chromatography (alumina, cyclohexane gradient ethyl acetate) followed by column chromatography (silica, cyclohexane gradient ethyl acetate) and thin layer chromatography (ethyl acetate) affords 0.167 g (14 %) of porphyrin **4b**. MS (FAB) m/z 1055 (M+1); UV($CH_2Cl_2$) $\lambda_{max}$ nm (log ε) 426 (5.45), 490 (3.67), 524 (4.02), 564 (4.11), 600 (3.63), 660 (3.72). $^1H$ NMR ($CDCl_3$) δ - 2.76 (s, 2 H, NH), 3.84 (s, 12 H, O$CH_3$), 5.28 (s, 8 H, *N*-$CH_2$), 7.00 (dd, 8 H, ar-H, *o*-$OCH_3$, *J* = 8.7 Hz), 7.47 (dd, 8 H, ar-H, *m*-$OCH_3$, *J* = 8.4 Hz), 8.11 (s, 4 H, pyrazole-$H_5$), 8.30 (s, 4 H, pyrazole-$H_3$), 9.02 (s, 8 H, pyrrole-$H_\beta$). $^{13}C$ NMR ($CDCl_3$) δ 55.86 (O$CH_3$), 56.57 (*N*-$CH_2$), 110.97 (C-*meso*), 114.98 (ar-$C_o$), 123.47 (pyrazole-$C_4$), 129.04 (ar-$C_p$), 129.99 (ar-$C_m$), 131.40 (pyrrole-$C_\beta$), 133.61 (ar-$C_i$ 1), 144.39 (2 C, pyrazole-$C_5$ and ar-$C_i$, 2), 160.17 (pyrazole-$C_3$). Anal. Calcd for $C_{64}H_{54}N_{12}O_4$: C, 72.85; H, 5.16; N, 15.93. Found: C, 72.79; H, 4.93; N, 15.69.

Meso-*tetrakis-(1-benzyl-5-methylpyrazol-3-yl)porphyrin* (**7b**).

The reaction was performed in 1 L of dichloromethane containing pyrazole **5b** (2.0 g, 10 mmol), pyrrole (0.69 mL, 10 mmol) and 2.5 M $BF_3.OEt_2$ (1.3 mL, 3.3 mmol), followed by oxidation with *p*-chloranil (2.71 g, 11 mmol) at reflux. Column chromatography (alumina, cyclohexane/ethyl acetate 2:1) followed by thin layer chromatography (ethyl acetate) affords 40 mg (1.6 %) of porphrin **7b**. $^1H$-NMR ($CDCl_3$): see discussion in the general part. MS (FAB): 990 (M); UV($CH_2Cl_2$) $\lambda_{max}$ nm (log ε) 420 (5.31), 518 (4.06), 552 (3.39), 592 (3.58), 650 (2.80). Anal. Calcd for $C_{64}H_{54}N_{12}$: C, 77.55; H, 5.53; N, 16.95. Found: C, 77.79; H, 5.73; N, 16.69.

Meso-*tetrakis{1-[2-(trimethylsilyl)ethoxymethyl]-3-methylpyrazol-5-yl}-porphyrin* (**8c**).

The reaction was performed with a mixture of pyrazole **5c+6c** (1.44 g, 6 mmol) and pyrrole (0.415 mL, 6 mmol) in dichloromethane (600 mL) and methanol (4.5 mL) using 2.5 M $BF_3.OEt_2$ (0.79 mL, 1.98 mmol) followed by oxidation with *p*-chloranil (1.1 g, 4.5 mmol) at reflux (1 h). Triethylamine (0.275 mL, 1.98 mmol) was added to neuralise the acid. Column chromatography on silica gel using cyclohexane/ethyl acetate 7:3 as eluent affords 0.27 g (4 %) of porphyrin **8c**. $R_f$ ($SiO_2$, cyclohexane/ethyl acetate 1:1) = 0.66. MS (EI) m/z 1151

(M+1). UV ($CH_2Cl_2$) $\lambda_{max}$ (log ε) 420 (5.22), 516 (3.93), 552 (3.58), 590 (3.42), 648 (3.11). $^1H$ NMR ($CDCl_3$) δ -2.88 (s, 2 H, N*H*), 0.10 [s, 36 H, Si($\underline{CH_3}$)$_3$], 1.12 (t, 8 H, $\underline{CH_2}$Si, *J* = 8.1 Hz), 2.65 (s, 12 H, pyrazole-$\underline{CH_3}$), 3.99 (t, 8 H, O$\underline{CH_2}$C, *J* = 8.3 Hz), 5.87 (s, 8 H, *N*-$\underline{CH_2}$O), 7.02 (s, 4 H, pyrazole-$\underline{H_4}$), 9.10 (s, 8 H, pyrrole-$\underline{H}\beta$). $^{13}C$ NMR ($CDCl_3$) δ : -1.23 [Si($\underline{C}H_3$)$_3$], 11.08 (pyrazole-5-$\underline{C}H_3$), 18.06 ($\underline{C}H_2$Si), 66.62 (O$\underline{C}H_2$C), 78.49 (*N*-$\underline{C}H_2$), 111.41 (ar-$\underline{C}$*meso*), 114.61 (pyrazole-$\underline{C_4}$), 130.83 (broad, pyrrole-$\underline{C}\beta$), 138.96 (pyrazole-$\underline{C_5}$), 145-150 (very broad, pyrrole-$\underline{C}\alpha$), 152.00 (pyrazole-$\underline{C_3}$). Anal. Calcd for $C_{60}H_{86}N_{12}O_4Si_4$: C, 62.57; H, 7.53; N, 14.59. Found: C, 62.22; H, 7.30; N, 14.22.

Meso-*tetrakis-[1-*(p-*methoxybenzyl)-3(5)-methylpyrazol-5(3)-yl]porphyrin* (**7d+8d**).

The reaction was performed in 700 mL of dichloromethane and methanol (3.5 mL), containing the mixture of **5d+6d** (1.61 g, 7.0 mmol), pyrrole (0.48 mL, 7.0 mmol) and 2.5 M $BF_3.OEt_2$ (0.9 mL, 2.3 mmol), after stirring 1 h at reflux, *p*-chloranil (1.89 g, 7.7 mmol) was added and the reflux continued for 1 h. Filtration over alumina (140 g, cyclohexane gradient ethyl acetate) followed by column chromatography (silica, cyclohexane gradient ethyl acetate) affords 0.204 g (10.6 %) of porphyrins **7d+8d**. MS (FAB): 1111 (M+1); UV ($CH_2Cl_2$) $\lambda_{max}$ (log ε) 424 (5.34), 520 (4.06), 556 (3.77), 592 (3.59), 650 (3.29). $^1H$ NMR ($CDCl_3$) δ -2.72 – -2.75 (2 s, 2 H, N$\underline{H}$), 2.58, 2.59, 2.69 (3 s, 12 H, pyrazole-$\underline{CH_3}$), 3.884, 3.888, 3.894 (3s, 12 H, O$\underline{CH_3}$), 5.663, 5.667, 5.672 (3s, 8 H, *N*-$\underline{CH_2}$), 6.19 - 6.33 (m, 4 H, ar-$\underline{H}$), 6.98 - 7.00 (m, 4 H, ar-$\underline{H}$), 7.04 - 7.06 (m, 8 H, ar-$\underline{H}$), 7.47-7.50 (m, 4 H, pyrazole-$\underline{H_4}$), 8.76-9.26 (m, 8 H, pyrrole-$\underline{H}\beta$).$^{13}C$ NMR ($CDCl_3$) (20 % **7d**, 80 % **8d**) δ 11.50, 11.60 (pyrazole-5-$\underline{C}H_3$ of **8d**), 14.09, 14.00 (pyrazole-3-$\underline{C}H_3$ of **7d**), 53.12 (*N*-$\underline{C}H_2$), 55.29, 55.41 (O$\underline{C}H_3$), several lines about 111 (pyrazole-$\underline{C_4}$), 114 (ar-C), 128 (ar-C), 138 (pyrazole $\underline{C_5}$ of **8d**), 143 (pyrazole $\underline{C_5}$ of **7d**), 147 (pyrazole $\underline{C_3}$ of **7d**), 151 (pyrazole-$\underline{C_3}$ of **8d**), 158 (ar-C). Anal. Calcd for $C_{68}H_{62}N_{12}O_4$: C, 73.49; H, 5.62; N, 15.12. Found: C, 73.31; H, 5.55; N, 15.08.

*5,10,15-Tris{1-[2-(trimethylsilyl)ethoxymethyl]-5-methylpyrazol-3-yl-}-20-(5-methylpyrazol-3-yl]}-porphyrin* (**16b**).

The SEM-protected porphyrin **8c** (0.15 g, 0.131 mmol) in ethanol (1 mL) was treated with 3 N aqueous HCl (5 mL) and the mixture was refluxed for 2 h. After evaporation of ethanol, the reaction mixture was cooled and neutralized with a saturated $K_2CO_3$ solution and extracted with dichloromethane. The solvent was evaporated and the residue purified by column chromatography on silica gel (cyclohexane gradient ethyl acetate) to affords a mixture of starting porphyrins **8c** (31 mg, 21 %) and partly deprotected porphyrin **16b** (19 mg, 14 %). Compound **16b**: $R_f$ ($SiO_2$, cyclohexane/ethyl acetate 1:1) = 0.24. MS (EI) m/z 1021 (M). UV ($CH_2Cl_2$) $\lambda_{max}$ (log ε) 417 (5.10), 518 (4.05), 556 (3.70), 592 (3.56), 650 (3.24). $^1H$ NMR ($CDCl_3$) δ -2.85 (s, 2H, N$\underline{H}$), 0.11 [s, 27 H, Si($\underline{CH_3}$)$_3$], 1.13 (t, 6 H, $\underline{CH_2}$Si, *J* = 8.1 Hz), 2.57 (s, 3 H, pyrazole-$\underline{CH_3}$), 2.76 (s, 9 H, pyrazole-$\underline{CH_3}$), 3.99 (t, 6 H, O$\underline{CH_2}$C, *J* = 8.2 Hz), 5.87 (s, 6 H, *N*-$\underline{CH_2}$O), 7.03 (s, 3 H, pyrazole-$\underline{H_4}$), 7.05 (s, 1 H, pyrazole-H$_4$), 9.11 (m, 2 H, pyrrole-$\underline{H}\beta$), 9.17 (m, 6 H, pyrrole-$\underline{H}\beta$). $^{13}C$ NMR ($CDCl_3$) δ : -1.25 [Si($\underline{C}H_3$)$_3$], 11.08 (pyrazole-5-$\underline{C}H_3$), 12.90 (pyrazole-5-$\underline{C}H_3$), 18.07 ($\underline{C}H_2$Si), 66.60 (O$\underline{C}H_2$C), 78.52 (*N*-$\underline{C}H_2$), 111.99 ($\underline{C}$*meso*), 112.67 (ar-$\underline{C}$*meso*), 114.61 (pyrazole-$\underline{C_4}$), 114.66 (pyrazole-$\underline{C_4}$), 130-132 (broad, pyrrole-$\underline{C}\beta$), 139.03 (pyrazole-$\underline{C_5}$), 144-148 (very broad, pyrrole-$\underline{C}\alpha$), 151.80 (pyrazole-$\underline{C_3}$), 151.87 (pyrazole-$\underline{C_3}$). Anal. Calcd for $C_{54}H_{72}N_{12}O_3Si_3$: C, 63.49; H, 7.10; N, 16.45. Found: C, 63.19; H, 7.40; N, 16.36.

Meso-*tetrakis-[3(5)-methylpyrazol-5(3)-yl]porphyrin* (**16a** = **7a** = **8a**)

Porphyrins **7d+8d** (150 mg, 0.135 mmol) and 4 mL TFAA under argon atmosphere were heated at reflux and under stirring for about 7 h. The magnet stirrer was washed with *ca* 4 mL dichloromethane and the solution evaporated to dryness. 5 mL water were added, extraction with dichloromethane (8 x 5 mL), the non soluble rest

was dissolved with glacial acetic acid. The dichloromethane phase was dried with $K_2CO_3$. The glacial acetic acid phase was evaporated to dryness and washed several times with dichloromethane/ cyclohexane 1:3, then centrifuged and decanted. Thus were obtained 6 mg of very pure material and from the dichloromethane phase, which was treated in the same way, 97 mg of product with a small amount of impurities. $^1$H NMR ($CD_3OD$) δ 2.99 (s, 12 H, pyrazole-$\underline{C}H_3$), 7.70 (s, 4 H, pyrazole-$\underline{H}_4$), 9.35 (s, 8 H, pyrrole-$\underline{H}_\beta$).$^{13}$C NMR ($CD_3OD$/TFAA) δ 11.15 (pyrazole-$\underline{C}H_3$), 115.67 (pyrazole$\underline{C}_4$), 115.75 ($\underline{C}$ *meso*), 130.13 (pyrrole-$\underline{C}_\beta$), 146.70 (pyrazole-$\underline{C}_5$), 158.84 (pyrazole-$\underline{C}_3$). MS (FAB) 630 (M); UV ($CH_3OH$) $\lambda_{max}$ (log ε) 416 (5.01), 510 (3.77), 548 (3.39), 588 (3.33), 644 (2.86). Anal. Calcd for $C_{36}H_{30}N_{12}$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.81; H, 4.62; N, 26.60.

Porphyrin **8c** (0.1 g, 0.087 mmol) in ethanol (2 mL) was treated with 3 N aqueous HCl (8 mL) and the mixture refluxed overnight. The cooled reaction mixture was neutralized with saturated $K_2CO_3$ solution. The solvent was evaporated and the residue extracted with ethanol to yield 0.04 g (73 %) of porphyrin **16a**. This compound was also prepared from **8c** (0.1 g, 0.087 mmol) and 2 mL of TFAA. After 2 h reflux, the crude mixture was evaporated to dryness, washed with dichloromethane and ethyl acetate. Yield of **16a** 0.045 g (82 %).

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