Molecular Recognition of Racemic Phosphines by a Chiral Ruthenium Porphyrin

Paul Le Maux, Hassan Bahri and Gérard Simonneaux

Laboratoire de Chimie Organométallique et Biologique, URA CNRS 415, Université de Rennes 1, 35042 Rennes Cedex, France

The preparation of ruthenium 'picket-fence' porphyrins bearing optically active α-methoxy-α-(trifluoromethyl)phenylacetyl residues on both sides of the porphyrin plane is described; chiral recognition in the complexation of racemic benzylmethylphenylphosphine to the α,β,α,β isomer leads to the formation of one of three possible product diastereoisomers with high stereoselectivity (>95%).

Cytochromes P450 have an active site able to recognise specifically their substrate.[1] Recently, mono[2] and di-oxygenase models[3] using chiral metalloporphyrins have been reported. By contrast, there is no report of a molecular recognition of a racemic substrate by chiral ruthenium porphyrin. We report now the separation of the diastereoisomeric ruthenium porphyrins obtained by complexation of racemic phosphines to the metal ion. Addition of an excess of benzylmethylphenylphosphine gave one of the three possible diastereoisomers consistent with the expected stereocontrol by the chiral porphyrin (>95%).

Coupling of the four atropisomers of *meso*-tetra(*o*-amino phenyl)porphyrin (tapp), in the thermodynamic ratio,[4] with Mosher's reagent [α-methoxy-α-(trifluoromethyl)phenyl-

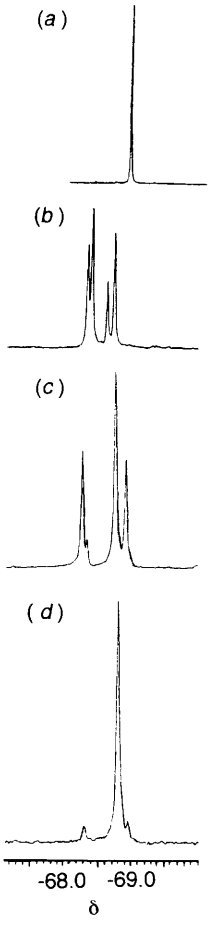


Fig. 1 ^{19}F NMR ($CDCl_3$) of (*a*) complex **3**, (*b*) complex **4**, (*c*) complex **5** after 3 h reaction and (*d*) complex **5** after immediate precipitation

acetyl chloride (mtpa)][5] yielded **1**† as a mixture of the four atropisomers (85% yield). Because the pickets isomerise at high temperatures (>150 °C) and a long reaction time is necessary for the insertion of ruthenium,[6] the mixture was used as obtained in further reactions. The ruthenium complex **2** was prepared by treatment of **1** with $Ru_3(CO)_{12}$ in *o*-dichlorobenzene at 180 °C (18 h).[6] In order to obtain a six coordinate ruthenium carbonyl mono L adduct, where L is a neutral ligand, tetrahydrofuran (THF) was added to the resulting solution before separation of the isomers. TLC on silica gel using diethyl ether–hexane–THF (100 : 100 : 1) as eluent gave excellent separations of four compounds, which are in the ratio 1.5 : 2 : 4 : 0.5 for α,β,α,β-**2a**, α,α,β,β-**2b**, α,α,β,β-**2c** and α,α,α,α-**2d**, respectively with the tetra α-atropisomer **2d** moving slowly (32% overall yield).‡ For the purpose of molecular recognition, it was decided that the α,β,α,β isomer offered the greater simplicity because the chiral pickets of this atropisomer provide a ruthenium molecule with two topologically identical faces. Confirmation that this was indeed the case came from the observation of the ^1H, ^{19}F and ^{31}P spectra of the bis-trimethylphosphine adduct: $Ru[P(Me)_3]_2(tapp)(mtpa)$ **3**. The PMe_3 complex displayed only a singlet (δ −68.9) [Fig. 1(*a*)] for the CF_3 groups of the four identical pickets, and a single ^{31}P resonance (δ −7.8) for the phosphine. In order to obtain diastereoisomeric ruthenium porphyrins, the red purple, six coordinate, low-spin complex Ru[P(Me)(Pr)(Ph)]$_2$ (tapp)(mtpa) **4**§ was first prepared from the precursor **2a** by treatment with the chiral phosphine (8 equiv.) in CH_2Cl_2 at room temperature (2 h, 76% yield). As expected, signals due to equivalent fluorines in the bis PMe_3 complex **3** are split in the complex **4** bearing the chiral phosphine [Fig. 1(*b*)]. The signals must represent the *R,R*-, the *R,S*- (two signals) and the *S,S*-diastereoisomers. Once this NMR non-equivalence pattern was recognized, we were able to separate each diastereoisomer by TLC (eluent:

† *Selected spectroscopic data* for **1a-d, 2a, 3, 4** and **5** NMR spectra were recorded (Brucker AC 300P spectrometer) in $CDCl_3$ at 300 MHz (^1H), 282 MHz (^{19}F with decoupling), 121 MHz, (^{31}P with decoupling). Satisfactory elemental analyses were obtained for compounds **1a, 2a, 3, 4** and **5**. Pure atropisomers **1a** (α,β,α,β), **1b** (α,α,β,β), **1c** (α,α,α,β) and **1d** (α,α,α,α) have been also obtained by separate experiments involving separation of the four atropisomers of *meso*-tetra(*o*-aminophenyl)-porphyrin[4] followed by coupling with Mosher's reagent.

1a, ^1H: δ −2.8 (s, 2H, NH pyrrole), 1.4 (s, 12H, OMe), 6.48 (br s, 20H, Ph picket), 8.58 (d, 4H, *J* 8.1 Hz, H-3), 7.90 (t, 4H, *J* 7.9 Hz, H-4), 7.65 (t, 4H, *J* 7.5 Hz, H-5), 8.07 (d, 4H, *J* 6.3 Hz, H-6), 8.02 (s, 4H, NHCO), 8.65, 8.83 (2s, 8H, β-pyrrole). ^{19}F: **1a**, δ −70 (s, $4CF_3$), **1b**, δ −69.92, −70.19 (2s, $4CF_3$), **1c**, δ −69.81, −70.07, −70.38, −70.81 (4s, $4CF_3$), **1d**, δ −70.69 (1s, $4CF_3$). VIS **1a–d** (CH_2Cl_2) : λ_{max}/nm 421 (ε 290 dm^3 $mmol^{-1}$ cm^{-1}), 513 (ε 40), 545 (ε 22), 589 (ε 23), 649 (ε 18).

‡ Except for **2a**, details of identification and spectral characteristics of these isomers will be described elsewhere.

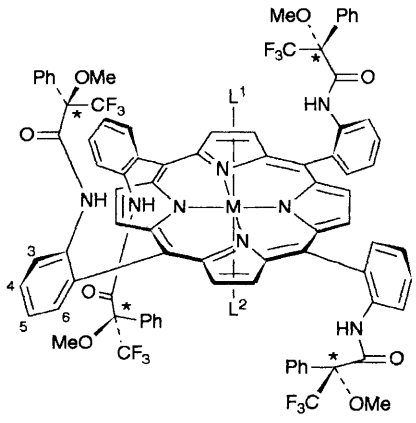
2a, ^1H : δ 1.53, 1.82 (2s, 12H, OMe), 6.76, 7.03 (2d, 8H, *J* 7.8 Hz, *ortho* Ph picket), 6.90, 7.19 (2t, 8H, *J* 7.8 Hz, *meta* Ph picket), 7.08, 7.29 (2t, 4H, *J* 7.3 Hz, *para* Ph picket), 8.67, 8.89 (2dd, 4H, J_1 7.9 Hz, J_2 < 1 Hz, H-3), 7.80, 7.83 (2td, 4H, J_1 7.2 Hz, J_2 1.4 Hz, H-4), 7.47, 7.51 (2td, 4H, J_1 7.4 Hz, J_2 1.3 Hz, H-5), 7.71, 7.74 (2dd, 4H, J_1 7.3 Hz, J_2 1.4 Hz, H-6), 8.21, 8.31 (2d, 4H, *J* 4.9 Hz, β-pyrrole), 8.57 (m, 4H, β-pyrrole), 8.38, 8.86 (2s, 4H, NHCO). ^{19}F : δ −69.36, −71.01 (2s, $4CF_3$). VIS (CH_2Cl_2) : λ_{max}/nm 410 (ε 187 dm^3 $mmol^{-1}$ cm^{-1}), 530 (ε 24). IR ν/cm^{-1} (CH_2Cl_2): 1960 (RuCO), 1270 (NHCO).

§ **3** was prepared by addition of an excess of 8 equiv. of PMe_3 to **2a** in CH_2Cl_2 (95% yield). ^1H: δ −2.65 (t, 18H, J_{HP} 2.8 Hz, Me_3P), 2.84 (s, 12H, OMe), 7.10–7.21 (m, 20 H, Ph picket), 8.87 (d, 4H, *J* 8.9 Hz, H-3), 7.69–7.75 (m, 8H, H-4, H-5), 7.35–7.37 (m, 4H, H-6), 7.79, 8.04 (2s, 8H, β-pyrrole), 8.88 (s, 4H, NHCO). ^{19}F: δ −68.92 (s, $4CF_3$). ^{31}P: δ −7.84 (s). VIS (CH_2Cl_2): λ_{max}/nm 440 (ε 175 dm^3 $mmol^{-1}$ cm^{-1}), 527 (ε 15).

4, Diastereoisomer *RR* (35%), R_f 0.52, ^1H : δ −2.59 (s, 6H, MeP), −2.61, −2.06 (2td, 4H, J_{HP} 160 Hz, J_{HH} 15 Hz, CH_2CH_2Me), −1.06, −0.74 (2 br m, 4H, J_{HP} 96 Hz, CH_2CH_2Me), 0.02 (t, 6H, *J* 7.1 Hz, $CH_2CH_2CH_3$), 2.85 (s, 12H, OMe), 4.08 (quin., 4H, *J* 3.7 Hz, *ortho* Ph phosphine), 6.15 (t, 4H, *J* 7.5 Hz, *meta* Ph phosphine), 6.60 (t, 2H, *J* 7.4 Hz, *para* Ph phosphine), 7.15 (m, 20 H, Ph picket), 8.86 (d, 4H, *J* 7.8 Hz, H-3), 7.67 (t, 4H, *J* 7.2 Hz, H-4), 7.25 (t, 4H, *J* 6.9 Hz, H-5), 6.72 (d, 4H, *J* 7.2 Hz, H-6), 7.69, 8.17 (2s, 8H, β-pyrrole), 9.18 (s, 4H, NHCO). ^{19}F: δ −68.42 (s, $4CF_3$). ^{31}P: δ 4.75 (s). VIS (CH_2Cl_2): λ_{max}/nm 441 (ε 150 dm^3 $mmol^{-1}$ cm^{-1}), 528 (ε 17). Diastereoisomer *RS* (51%), R_f 0.45, ^1H : δ −2.65, −2.60 (2 br s, 8H, MeP, CH_2CH_2Me), −2.06 (br m, 2H, CH_2CH_2Me), −1.07, −0.73 (2 br m, 4H, CH_2CH_2Me), −0.20, 0.02 (2t, 6H, $CH_2CH_2CH_3$). ^{19}F : δ −68.34, −68.74 (2s, $4CF_3$). ^{31}P : δ 5.1 (s). Diastereoisomer *SS* (14%), R_f 0.38, ^1H : δ −2.65 (s, 6H, MeP), −2.57, −2.14 (2td, 4H, J_{HP} 129 Hz, J_{HH} 15 Hz, CH_2CH_2Me), −1.12, −0.76 (2 br m, 4H, J_{HP} 108 Hz, $CH_2CH_2CH_3$), −0.23 (t, 6H, *J* 7.2 Hz, $CH_2CH_2CH_3$), 2.71 (s, 12H, OMe), 4.16 (quin, 4H, *J* 3.7 Hz, *ortho* Ph phosphine), 6.55 (t, 4H, *J* 7.5 Hz, *meta* Ph phosphine), 6.85 (t, 2H, *J* 7.4 Hz, *para* Ph phosphine), 7.21-7.39 (m, 20H, Ph picket), 8.79 (d, 4H, *J* 8.1 Hz, H-3), 7.66 (t, 4H, *J* 7.2 Hz, H-4), 7.33 (t, 4H, *J* 7 Hz, H-5), 6.72 (d, 4H, *J* 7.3 Hz, H-6), 7.89, 7.96 (2s, 8H, β-pyrrole), 9.34 (s, 4H, NHCO). ^{19}F : δ −68.63 (s, $4CF_3$). ^{31}P : δ 4.91 (s).

5, Diastereoisomer *SS*, ^1H : δ −2.98 (s, 6H, MeP), −1.44, −0.68 (2 br d, 4H, J_{HP} 228.1 Hz, J_{HH} 14.5 Hz, CH_2Ph), 2.69 (s, 12H, OMe), 3.98 (m, 4H, *ortho* Ph phosphine) 4.88 (d, 4H, *J* 7.7 Hz, *ortho* Ph benzyl), 6.37–6.93 (m, 16H, *meta* + *para* Ph phosphine, *meta* + *para* Ph benzyl), 8.81 (d, 4H, *J* 8.3 Hz, H-3), 7.67 (t, 4H, *J* 7.3 Hz, H-4), 7.09–7.25 (m, 28H, H-5, H-6, Ph picket), 7.90, 8.04 (2s, 8H, β-pyrrole), 9.39 (br s, 4H, NHCO). ^{19}F : δ −68.78 (s, $4CF_3$). ^{31}P : δ 4.41 (s). VIS (CH_2Cl_2): λ_{max}/nm 440 (ε 91 dm^3 $mmol^{-1}$ cm^{-1}), 526 (ε 16).

Diastereoisomers *RS* and *RR* have not been isolated. However, their ^{19}F NMR chemical shifts have been assigned: δ −68.3 and −68.9 for *RS*, δ −68.36 for *RR*.



1; M = H_2
2; M = Ru, L^1 = CO, L^2 = THF
3; M = Ru, $L^1 = L^2 = PMe_3$
4; M = Ru, $L^1 = L^2$ = PMePhPr
5; M = Ru, $L^1 = L^2 = PCH_2PhMePh$

toluene–diethyl ether 100 : 1). Although the integration of the NMR signals indicates only a weak preference for a particular configuration (*R*) (preference per binding site: *R*/*S* = 1.5), the absolute configuration of the chiral phosphine in the diastereoisomers was assigned after determination of the configuration of the free phosphine recovered at the end of the reaction (*S*).[7]

In contrast, complexation of racemic benzylmethylphenylphosphine to the chiral ruthenium porphyrin **2a** leads to the compound Ru[P(Me)(CH_2Ph)(Ph)]$_2$(tapp)(mtpa) **5**§ with chiral recognition. In a typical experiment, reaction of **2a** (35 mg, 0.02 mmol) with the phosphine (8 equiv.) at 25 °C for 3 h in CH_2Cl_2 (10 ml) under nitrogen gave a 50 : 45 : 5 mixture of the three diastereoisomers (*SS*/*RS*/*RR*, respectively) (preference per binding site: *S*/*R* = 2.6) [Fig. 1(*c*)]. Moreover, an immediate precipitation with an excess of hexane, after phosphine addition, provided a diastereoisomer of **5** with high purity (>95%) (preference per binding site: *S*/*R* = 39) as assessed by 300 Mz ^{1}H and ^{19}F NMR spectroscopy (95% overall yield from **2a**) [Fig. 1(*d*)]. After work-up and chromatographic separation from **5** on silica column (eluent : toluene) under nitrogen, the excess of P(Me)(CH_2Ph)(Ph) was recovered with the *R* configuration.[8] This result unambiguously established the configuration of the phosphine in **5** as *S*,*S*. The source of the high stereoselectivity observed in the latter reaction is attributed to steric effects. It is mainly the preferred mode of the initial binding of the chiral phosphine to the ruthenium porphyrin that determines the chiral recognition. Longer reaction times favour formation of the other isomers. For instance, addition of six equivalents of racemic P(Me)(CH_2Ph)(Ph) to *S*,*S*-**5** in CH_2Cl_2 at 25 °C gave the above mixture (50 : 45 : 5) of the three diastereoisomers after 3 h.

The effectiveness of the chiral ruthenium porphyrin **2a** as an haemoprotein model capable of chiral recognition reactions has been demonstrated.

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