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Illustrating atropisomerism in the porphyrin series using NMR spectroscopy

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Abstract. The existence of biphenyl-type atropisomerism in porphyrins has been known for more than twenty-five years. Over the last two decades, different examples of this type of stereoisomerism have been reported in the literature with regard to the use of synthetic metalloporphyrin complexes as models of heme-containing enzymes. In this article, we present a clear ^{1}H NMR study to illustrate the concept of atropisomerism in the porphyrin series. The example is based on a porphyrin substituted in the *meso* positions by sulfonatomesityl groups such that the two methyls in both *ortho* positions restrict the rotation about the aryl-porphyrin C-C bond and the sulfonate group in the *meta* position clearly resolves the ^{1}H resonances of the two *ortho* methyls. This analysis allows visualization and unambiguous check of the statistical distribution of the different atropisomers.

Key words. Porphyrin – analytical chemistry – NMR spectroscopy – atropisomerism.

Atropisomers are stereoisomers resulting from restricted rotation around single bonds such that the rotational barrier is high enough to permit observation of the isomeric species. Atropisomers are numerous in number and type: among atropisomers of the sp^2–sp^2 single bond type, a classical example is constituted by the biphenyls (or biaryls in general) as shown in figure 1A. When $X \neq Y$ and $U \neq V$ and if the steric interaction of *X–U*, *X–V*, and/or *Y–V*, *Y–U* is large enough, two nonplanar, axially chiral enantiomers exist [1]. Another example of atropisomerism, related to the biphenyl-type, was first reported by Gottwald and Ullman in the porphyrin series (Fig. 1B) [2]. This type of atropisomerism in porphyrins has been utilised in the design of superstructured models of the active sites of hemoproteins [3-7].

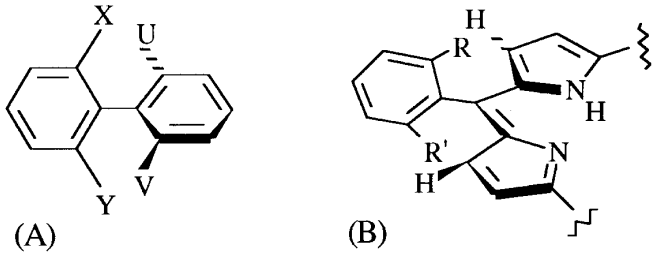

Fig. 1. Biphenyl-type atropisomerism.

Porphyrins (see Fig. 3) are macrocycles consisting of four pyrroles linked by four methine bridges. Carbons *5*, *10*, *15* and *20* are designated *meso* and carbons 2, 3, 7, 8, 12, 13, 17 and 18 are the β pyrrole positions (Fisher's convention [8]). Porphyrins with four identical aryl groups in the *meso* position are derivatives with restricted rotation about the aryl-porphyrin bond due to interactions of the β-CH groups with the *ortho*-substituents of the *meso*-aryl groups (*R* or *R'* ≠ H, *R* and *R*' magnetically nonequivalent, Fig. 1B). At room temperature, the conformational rigidity is frequently sufficient to observe and also to isolate the corresponding atropisomers. These isomers may be described in terms of whether the *ortho* substituents are above (β) or below (α) the plane of the porphyrin ring [9]. When the porphyrin ring is formed by random linkages of pyrroles and mono-*o*-substituted benzaldehydes, the statistical ratio for the four possible isomers β_4, $\alpha\beta_3$, $\alpha_2\beta_2$ and $\alpha\beta\alpha\beta$ is 1:4:2:1, respectively (Fig. 2). Gottwald and Ullman [2] separated these isomers by chromatography in their study on *meso*-tetrakis(*o*-hydroxyphenyl)porphyrin. Recently, the structure of two atropisomers was assigned based on X-ray analysis [10]. The distribution of the four atropisomers was estimated in the case of the nickel complex of *meso*-tetra-*o*-tolylporphyrin (*R* = Me, *R*' = H, Fig. 1B) by visual comparison of the areas of the six types of methyl group resonances [11]. According to other studies on porphyrins (see references [3-5] and [12-19] for a representative list of examples), the existence of atropisomers is usually revealed in NMR spectroscopy by multiplets with rather broad peaks mainly due to extensive overlap of signals.

To clearly illustrate atropisomerism, we discuss the well-resolved 250 MHz ^{1}H NMR spectrum of *meso*-tetrakis(3-sulfonatomesityl)porphyrin tetrasodium salt (Fig. 3), a porphyrin prepared (note 1) as a potential antiviral agent [20]

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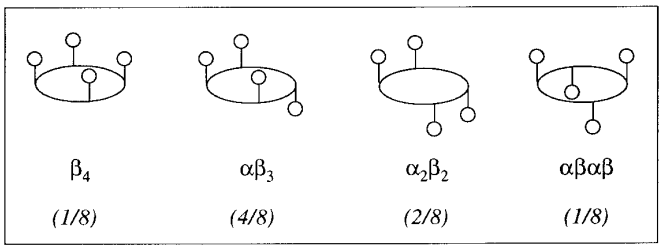

Fig. 2. Four possible atropisomers with mention of the statistical ratio.

and developed as a biomimetic oxidation catalyst [21]. We chose this example for the following reasons:

– the mesityl ring introduced in the *meso* positions of the porphyrin has methyl substituents in both *ortho* positions of the phenyl group, which greatly increases the activation energy of the rotation barrier around the C-C bond diminishing the possibility of thermal isomerization [12].

– only one chlorosulfonation site (from one of the two possible) in the *meta* positions of the mesityl was obtained under our experimental conditions and was responsible (after having been converted in sulfonate group) for creating atropisomerism in this structure with a perfect stastistical distribution of atropisomers.

– the strong electron-withdrawing effect of the sulfonate group provides good resolution of the methyl signals in each mesityl ring. Although the precursor *meso*-tetrakis[3-(chlorosulfonyl)mesityl]porphyrin has the theoretical structural features, it does not constitute a suitable example since the six peaks of the ortho methyl protons are not as well resolved.

Figure 3 shows the 250 MHz NMR spectrum of *meso*-tetrakis(3-sulfonatomesityl)porphyrin tetrasodium salt in DMSO. Only the *ortho* methyl proton peaks are well resolved for all four atropisomers. Assignments, consistent with the theoretical statistical distribution of atropisomers (Fig. 2), are indicated in figure 3. The following key points support this assertion:

1) The pyrrole β-protons resonances, (a), appear as two equal intensity peaks (4H each) at 8.68 and 8.66 ppm. Evidently, two families of pyrrole β-protons are defined by the orientation of the surrounding mesityl substituents: the first set of pyrroles with adjacent $\alpha\alpha$ (or $\beta\beta$) sulfonatomesityls and the second set with adjacent $\alpha\beta$ (or $\beta\alpha$) sulfonatomesityls. In both cases, the two pyrrole β-protons are magnetically equivalent.

2) The N-H resonance for all atropisomers is observed as a rather broad, unresolved signal at –2.41 ppm.

3) The resonance of the mesityl ring protons, (b), is a singlet (4H) at 7.42 ppm.

4) The resonance of the *para* methyl protons, (c), is a singlet (12 H) at 2.99 ppm. This chemical shift is mainly influenced by the adjacent sulfonate group and not by the other mesityls, at least at the level of sensitivity of this analysis.

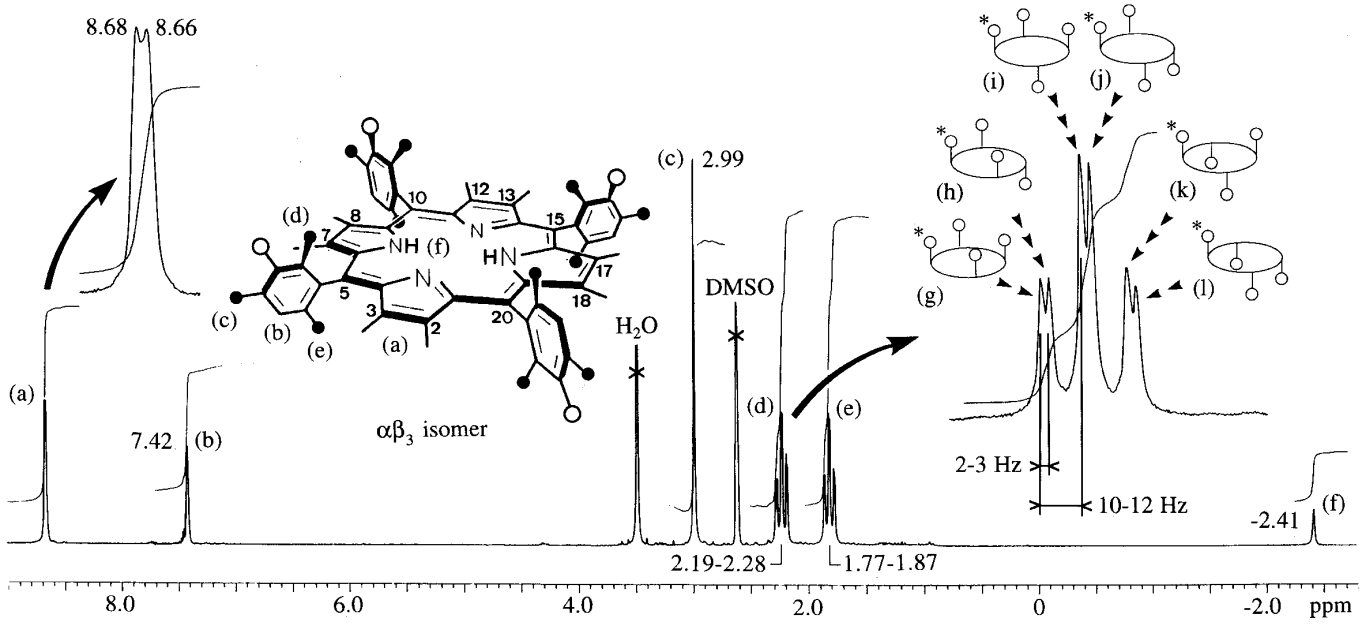

Fig. 3. A representative 250 MHz ^{1}H-NMR spectrum and assignments of signals of a statistical atropisomer mixture of *meso-tetrakis*(3-sulfonatomesityl)porphyrin tetrasodium salt. ♀ sulfonate groupe, ❦ methyl group, * location of the methyl group (d) responsible for the indicated resonance.

5) The resonance of each type of *ortho* methyl protons, (d) or (e) (12H each), resemble a triplet split into a doublet. Each multiplet, however, is a set of six singlets. These two distinct methyl groupings, sets (d) at 2.19 – 2.28 ppm and (e) at 1.77 – 1.87 ppm, allow straightforward analysis of the atropisomer mixture. The downfield set of peaks (d) is assigned to the methyl protons adjacent to the sulfonate group by assuming that the electronic-withdrawing effect of the mesitylsulfonate groups deshield *o*-methyl protons more effectively than *p*-methyl protons. The statistical distribution of the four atropisomers (Fig. 2) and the six different types of *ortho* methyl protons (Fig. 3) predicted a 1:1:2:2:1:1 relative intensities for the six peaks (see note 2) [11]. The very similar upfield set of peaks at 1.77 – 1.87 ppm (e) is assigned to the methyl protons *para* to the sulfonate group, and each peak assignment was made on the same assumption and predicted relative intensities. Within each family (d) or (e), a given methyl group (indicated by an asterisk in figure 3) will be more deshielded as the number (one, two or three) and the proximity (adjacent or opposite) of the sulfonate groups on the same face of the porphyrin macrocycle increase. The deshielding effect is 0.04 – 0.05 ppm (10 – 12 Hz at 250 MHz) for a cofacial sulfonate group present in an adjacent mesityl or # 0.01 ppm (2 – 3 Hz) for one present in an opposite mesityl. These effects are additive. The statistical distribution of atropisomers (Fig. 2) and the six different possible environments for each methyl group, noted (g) to (l) (Fig. 3, note 2) account for the intensity ratios of the different peaks. The different types of methyls (d) observed in figure 3 are present in atropisomers β_4, type (g), $\alpha\beta_3$, types (*h*)+(*i*)+(*l*), $\alpha_2\beta_2$, type (*j*) and $\alpha\beta\alpha\beta$, type (*k*). The intensities of the six related signals are in good agreement with the predicted statistical distribution 1:1:2:2:1:1 (see note 2).

In conclusion, the NMR analysis presented here provides an example of a clear and easy identification of the four possible atropisomers that can be observed in an idealized distribution in porphyrin series.

Notes

1. The precursor *meso*-tetrakis[3-(chlorosulfonyl)mesityl] porphyrin was prepared from *meso*-tetramesitylporphyrin and chlorosulfonic acid [21]. The crude product (about 50 mg) was then refluxed for 3 h with 50 mL 0.1 M HCl. After cooling to r.t. and neutralization with 1 M NaOH to pH 8, the solvent was evaporated to dryness giving a violet solid residue, which was directly submitted for NMR analysis.

2. The statistical ratio of atropisomers β_4, $\alpha\beta_3$, $\alpha_2\beta_2$ and $\alpha\beta\alpha\beta$ is classically $\underline{1}:\underline{4}:\underline{2}:\underline{1}$ [11]. If we now consider the methyl groups (d) (adjacent to the sulfonate group, see Fig. 3) which give multiple resonances from 2.19 to 2.28 ppm, the statistical analysis is as indicated in table I.

The analysis is the same for the methyl groups (e) (in the *para* position with respect to the sulfonate group) which give six signals ranging from 1.77 to 1.87 ppm.

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Table I.

– atropisomer β_4, statistical frequency = $\underline{1}$		
4 equivalent methyls:	type (g) = $\underline{1} \times 4$;	relative intensity 1
– atropisomer $\alpha\beta_3$, statistical frequency = $\underline{4}$		
3 types of methyls:	type (h) = $\underline{4} \times 1$;	relative intensity 1
	type (i) = $\underline{4} \times 2$;	relative intensity 2
	type (l) = $\underline{4} \times 1$;	relative intensity 1
– atropisomer $\alpha_2\beta_2$, statistical frequency = $\underline{2}$		
4 equivalent methyls:	type (j) = $\underline{2} \times 4$;	relative intensity 2
– atropisomer $\alpha\beta\alpha\beta$, statistical frequency = $\underline{1}$		
4 equivalent methyls:	type (k) = $\underline{1} \times 4$;	relative intensity 1

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