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Selective formation of either Tröger's base or spiro Tröger's base derivatives from [2-aminoporphyrinato(2-)]nickel by choice of reaction conditions

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ABSTRACT

The article reports on the unique manipulation of the acid-catalyzed reaction of [2-aminoporphyrinato (2-)]nickel with formaldehyde to form selectively either the symmetric Tröger's base or the asymmetric spiro Tröger's base bis(metalloporphyrin) derivative. The reaction is driven by the choice of acid catalyst, formaldehyde source, and particularly, solvent, to give a mixture of both derivatives in preparative yields of about 90%, or to give selectively one of the derivatives in a yield of about 60%.

Metalloporphyrins are essential for the vitality of bacteria, fungi, plants, and animals, and they have been the subject of many studies over several decades.[1] In addition, there have been numerous attempts by chemists to utilize the properties of metalloporphyrins in artificial systems.[2] An important area of research and development involves molecules possessing two metalloporphyrin units in a specific spatial position, which enables their cooperation.[1–3]

Crossley's research group has recently shown that two metalloporphyrin units can be connected by a Tröger's base (TB) structural skeleton[4] to form rigid V-shaped molecules, for example, metalloporphyrin TB **1** (Fig. 1).[5] The metalloporphyrin units in a TB derivative are held in a rigid position, which enables their cooperation that results in the selective binding of bidentate molecules, such as diamines.[5,6] Optically pure enantiomers of metalloporphyrin TB exhibit excellent stereoselective binding of histidine and lysine esters.[7,8] With extended porphyrins, the metal–metal distance is extended, and thus, the selectivity.[9]

The current methods for preparing TB **1** are not perfect. As the initial aminoporphyrin **2** is prepared by the nitration of metalloporphyrin **3**, followed by demetalation and reduction,[10] it is obvious that direct conversion of aminometalloporphyrin **4** into TB **1** would save two reaction steps. Unfortunately, while aminoporphyrin **2** yielded the corresponding TB **5** in a 73% yield, the

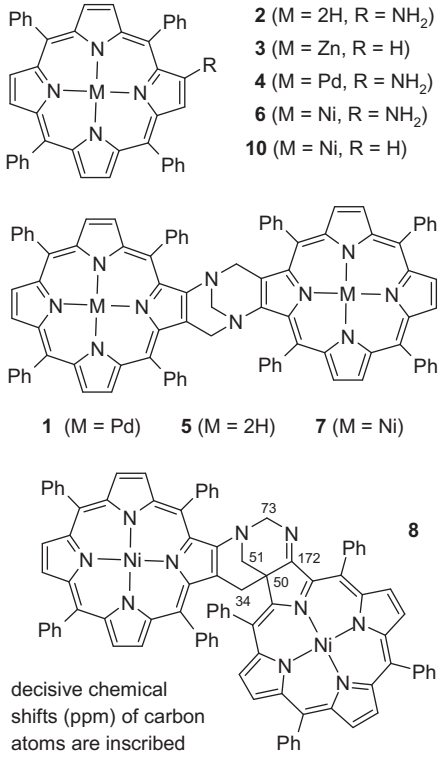

Figure 1. Structures of discussed porphyrin derivatives.

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Table 1
Preparative yields of TB **7** and spiroTB **8** at various conditions

	Reaction solvent	Source of formaldehyde	Acid	Reaction temperature (°C)	Reaction time (h)	Yield of TB **7** (%)	Yield of spiroTB **8** (%)
a	THF	Formalin	HCl	60	20	16	Trace
b	THF	Formalin	HCl	25	1	32	Trace
c	THF	Formalin	HCl	25	20	29	Trace
d	THF	Formalin	HCl	−20	2	16	Trace
e	THF	Formalin	HCl	−20	9	15	Trace
f	THF/$CHCl_3$ 99:1	Formalin	HCl	25	20	39	Trace
g	THF/$CHCl_3$ 1:1	Formalin	HCl	25	20	43	16
h	THF/$CHCl_3$ 1:99	Formalin	HCl	25	20	13	77
i	$CHCl_3$	Formalin	HCl	25	20	19	70
j	$CHCl_3$	Formalin	HCl	25	1	13	69
k	$CHCl_3$	Formalin	HCl	−20	2	14	61
l	1,4-Dioxane	Formalin	HCl	25	20	56	Trace
m	CH_2Cl_2	Formalin	HCl	25	20	17	50
n	$CHCl_3$	Formalin	TFA	25	20	32	43
o	$CHCl_3$	HMTA	TFA	25	20	Not observed	Trace
p	TFA	HMTA	TFA	25	20	Not observed	Not observed
q	$CHCl_3$	HMTA	HCl	25	20	Not observed	67

direct conversion of the aminometalloporphyrin **4** into TB **1** gave only a 29% yield.[5]

As we intend to utilize metalloporphyrins as the binding units of molecular tweezers, based on bis-Tröger's base derivatives,[11,12] we performed a brief study of the direct conversion of the aminometalloporphyrin **6** into TB **7** (Fig. 1). We found that the conversion of **6** into TB **7** is followed by the formation of the more polar spiroTB **8** (the only recently reported type[13] of constitutional isomer of TB), where the yields of TB **7** and spiroTB **8** are highly influenced by the reaction conditions (Table 1). Demetalation was not observed in any case because neither signals near −3 ppm in the ^{1}H NMR spectra nor extra spots of expected polarity on TLC were observed.

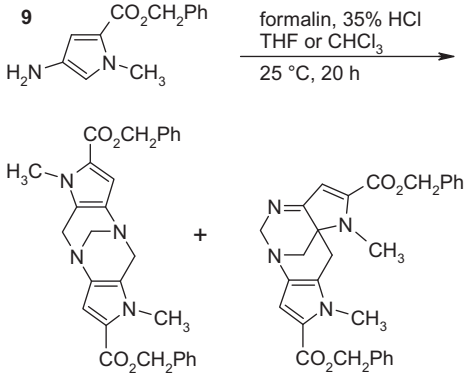
First, we applied conditions that were similar to those published by Crossley.[5] Specifically, nickelporphyrin **6** was treated with formalin and hydrochloric acid in THF at 60 °C for 20 h to give a 16% yield of TB **7** (row a). Lowering the reaction temperature to 25 °C doubled the yield; however, further reducing the reaction temperature to −20 °C still produced only a 16% yield. In both cases with a reduced reaction temperature, extending the reaction duration did not affect the yields (rows b-e). In all cases, TB **7** was accompanied by traces of spiroTB **8**.

We explored how a solvent affects the reaction yield. When a 99:1 volume ratio of THF/$CHCl_3$ was used, the yield of TB **7** increased, and spiroTB **8** was still present in trace amounts (row f). However, when a higher content of $CHCl_3$ was used, the yield of spiroTB **8** increased dramatically to approximately 70% (rows g–i). In contrast to the reaction in THF (rows a–e), when the reaction was performed in $CHCl_3$, the yields of TB **7** and spiroTB **8** were barely affected by temperatures (rows i–k).

Next, we discovered that similar solvents behave similarly. The replacement of THF by 1,4-dioxane significantly increased the yield of TB **7** to 56%, while spiroTB **8** remained a trace byproduct (row l). The replacement of $CHCl_3$ with CH_2Cl_2 did not affect the yield of TB **7**; however, the use of CH_2Cl_2 notably decreased the yield of spiroTB **8** to 50% (row m).

Finally, we evaluated the influence of the acid catalyst and the formaldehyde source. The use of TFA instead of hydrochloric acid decreased the total yield, although the yield of TB **7** notably increased (rows n vs. i). Surprisingly, using hexamethylenetetramine (HMTA) and TFA, which are the standard conditions that are used for TB preparation,[4,12] yielded only complex mixtures, even when TFA was used as the solvent (rows o–p). Conversely, when HMTA and hydrochloric acid were used, the formation of TB **7** was completely suppressed, and the yield of spiroTB **8** remained high (rows q vs. i).

To determine whether the effect of the solvent is specific to porphyrins, we used naphth-2-ylamine, which is known to form both a TB and a spiroTB,[13] and aminopyrrole **9** (Scheme 1), which is closely related (in structure) to porphyrins and known to form TB.[14] These amines were treated with formalin and hydrochloric acid at 25 °C for 20 h in THF or $CHCl_3$. The treatment of naphth-2-ylamine yielded only the corresponding TB, regardless of the solvent used (71% in THF, 73% in $CHCl_3$); the formation of the corresponding spiroTB was not observed. In contrast, aminopyrrole **9** produced the corresponding TB in high yield (84%) with minor



Scheme 1. The expected products of aminopyrrole **9.**

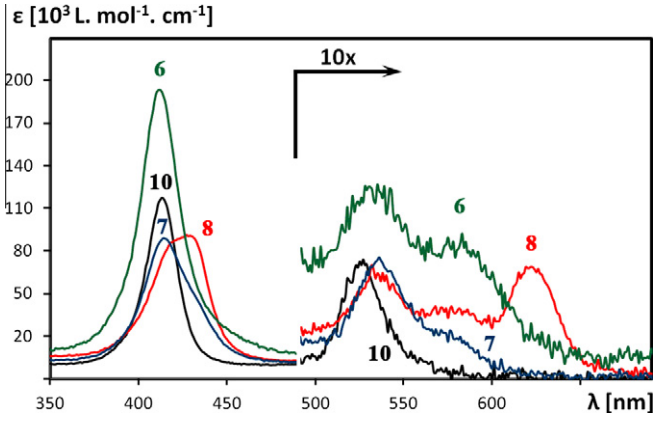


Figure 2. UV–Vis spectra in CH_2Cl_2: **6** (green), **7** (blue), **8** (red), and **10** (black).

byproducts generated when THF was used; however, the treatment in $CHCl_3$ yielded TB in a 34% yield with many byproducts. Unfortunately, we were unable to resolve the structures of these byproducts; however, none of the byproducts exhibited ^1H or ^{13}C NMR features that are characteristic of spiroTB derivatives.

In spite of making many attempts, we were unsuccessful in preparing single-crystals that were suitable for X-ray diffraction. Fortunately, the NMR characteristics are known for both metalloporphyrin TBs[15] and spiroTB structural motifs.[13] Thus, detailed analyses of 1D and 2D NMR spectra were sufficient to confirm the structures.

Both porphyrin TB **7** and spiroTB **8** have *m/z* values for the molecular ion and isotope cluster that correspond to the summary formula $C_{91}H_{59}N_{10}Ni_2$ (MH^+); however, because TB **7** has C_2 symmetry, only half of the signals are distinguished in its ^1H and ^{13}C NMR spectra, in contrast to the asymmetry observed in spiroTB **8**. Consequently, TB **7** has only one AB system for the porph-CH_2-N groups (3.80 and 3.66 ppm, $^2J_{HH}$ = 17.4 Hz) and a singlet for N-CH_2-N group (4.66 ppm), where the corresponding carbon atoms are at 54.6 and 67.3 ppm, 'respectively'. Conversely, spiroTB **8** has NMR spectral features typical of a spiroTB structural motif:[13] (a) three AB systems at 4.22 and 4.10 ppm ($^2J_{HH}$ = 18.2 Hz), 3.65 and 2.92 ppm ($^2J_{HH}$ = 12.1 Hz), and 3.07 and 2.92 ppm ($^2J_{HH}$ = 17.7 Hz), whereas the corresponding carbon atoms are at 72.9, 50.9, and 33.8 ppm; and (b) characteristic signals of ^{13}C at 49.5 ppm (spiro carbon) and 172.0 ppm (imine carbon).

An investigation of the UV–vis spectra (Fig. 2) revealed that TB **7** has a Soret band at 414 nm (similar to that of the initial porphyrinatonickel **10** and aminoporphyrinatonickel **6**) but with a small shoulder at a higher wavelength. In contrast, spiroTB **8** has a Soret band at a higher wavelength (429 nm) with a distinct shoulder at a lower wavelength. The Soret band of dimer **8** with a shoulder can be attributed to the presence of two types of porphyrin units, as well as to the exciton coupling between them. The Q-band of TB **7** at 536 nm is accompanied by a shoulder at approximately 576 nm, which is similar to aminoporphyrinatonickel **6**. These two Q-bands are also found in spiroTB **8** at similar wavelengths. SpiroTB **8** also has an extra Q-band at 622 nm, which could be attributed to the metalloporphyrin unit containing the spiro sp^3 carbon.

As is characteristic for porphyrinatonickel derivatives,[16] we did not observe fluorescence of either **7** or **8**.

To resolve the enantiomers of TB **7** and spiroTB **8** on an analytical scale, we used an HPLC column Reprosil Chiral NR with a Whelk O1 type chiral phase, which is generally efficient in resolving TB derivatives.[17] Surprisingly, we found no conditions that could resolve TB **7**. Conversely, spiroTB **8** was resolved under almost any conditions we applied, with the best conditions giving selectivity, α, of 1.77 and a resolution, R_S, of 2.35.

In summary, we have discovered a unique way to manipulate the reaction of aminoporphyrinatonickel **6** with formaldehyde and an acid to form selectively either metalloporphyrin TB **7** (56% yield) or spiroTB **8** (67% yield) or to form a mixture of both with 90% yields. Such manipulation of this reaction is unique; however, as the experiment with a pyrrole derivative **9** suggests, the reaction is not limited to metalloporphyrin substrates, though we believe that coordination of the solvent to the metal center could be an important factor. Additional research is needed to understand better the mechanisms underlying the reaction.

In addition, we have prepared a new type of metalloporphyrin dimer, spiroTB, which can alter the unique properties of metalloporphyrin TBs.[5–9] Particularly, the different behaviors of TB **7** and spiroTB **8** on a chiral HPLC column suggest that the two molecules will behave differently in chiral applications. Another use of spiroTB can arise from the presence of two metalloporphyrin cores with different spectral properties that are rigidly anchored in a molecule.

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Supplementary data

Supplementary data (Detailed preparations, analyses of NMR spectra, UV–vis spectra and chiral separations are provided as supplementary material) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.097.

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