Transition Metal Complexes with the Proton Sponge 4,9-Dichloroquino[7,8-*h*]quinoline: Highly Twisted Aromatic Systems and an Extreme "Out-of-Plane" Position of the Coordinated Transition Metal Atom**

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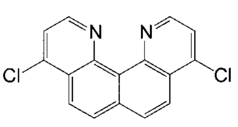
Dedicated to Professor Heinz A. Staab
on the occasion of his 75th birthday

We report the first successful synthesis and complete characterization of transition metal complexes of the "proton sponge" 4,9-dichloroquino[7,8-*h*]quinoline **1**. The novel proton sponge **1** and its derivatives were prepared and described fifteen years ago by Zirnstein and Staab.[1, 2] Even at that time these strong bases already had a complicated and controversial history: Although several authors had reported the synthesis of these compounds, the products were incorrectly formulated.[3, 4] To our knowledge, all attempts to synthesize stable metal complexes with proton sponges as ligands have been unsuccessful.



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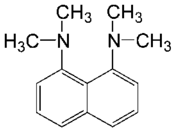

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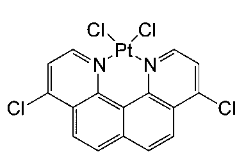
The first proton sponge, 1,8-bis(dimethylamino)naphthalene **2**,[5] is not suitable as a ligand for metal complexes because the methyl groups shield the nitrogen atoms and thereby sufficient thermodynamic stability is not conferred on the complex that could be formed.[6] Although 1,8-diaminonaphthalene[7, 8] is not a proton sponge a few transition metal complexes are known.

The proton sponge **1**, in contrast, is a molecule in which the complexing nitrogen atoms are part of the aromatic system. In addition, this compound is planar and not helical and thus very suitable as a ligand for metal complexes. **1** is in comparison a better ligand than the widely used *o*-phenanthroline for two reasons: The unusually high basicity of **1** (p$K_a = 10.9$[8]) compared to *o*-phenanthroline (p$K_a = 4.81$[9]) and the short nitrogen–nitrogen distance of 2.685 Å forces the complexed metal atom into an "out-of-plane" position. This confers a very high thermal stability on the metal complexes. The extreme "out-of-plane" position of the metal atom leads to a very reactive, accessible metal center and exposes one side for a variety of interactions including substitution and addition reactions. Compounds with such strong "out-of-plane" conformations are now a "hot" research theme.[10–12]

The small nitrogen–nitrogen distance along with the high basicity of **1** limits the use of protic solvents in the metal complex synthesis. However, dichloromethane or chloroform are suitable for the formation of the platinum and palladium complexes **3** and **4**, and THF for the rhenium and manganese complexes **5** and **6**. The synthesis of the platinum complex **3** was successfully completed by treating Zeise's dimer $[Pt_2(H_2C{=}CH_2)_2Cl_4]$ in dichloromethane with compound **1**. The complex precipitated as a yellow solid. The X-ray molecular analysis revealed a very unusual structural feature: The aromatic system is strongly bowed (Figure 1). The extent of the bowing can be determined by measuring the deviation



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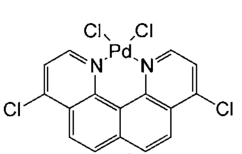

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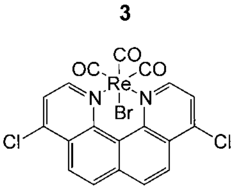

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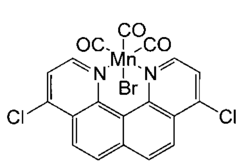

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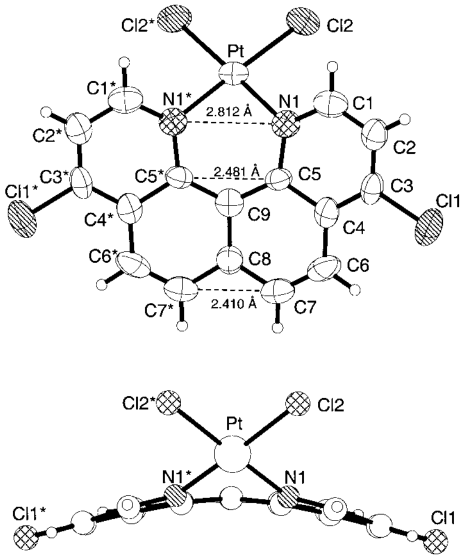

Figure 1. Diamond plot of **3** in front and side view.

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of the lowest and highest atoms of the aromatic system from a "best" plane. This plane results when the sum of the squared deviations of all single carbon and nitrogen atoms from the aromatic system is minimized. For example, the ligand atoms N1(−0.359 Å) and C3 (0.383 Å), which lie farthest outside this plane, define the bend of the bow: 0.742 Å. The corresponding value for the nearly planar ligand **1** is 0.151 Å. The central platinum atom assumes an extreme "out-of-plane" position relative to the best plane and lies 1.43 Å over this plane. In spite of this, the platinum atom is coordinated in a square planar environment that is relatively undisturbed.

The rhenium complex was prepared by heating the ligand in THF with the prepared rhenium(I)tetracarbonylbromide dimer. The distance from the rhenium atom to the "best" plane is 1.42 Å which is similar to that of the platinum atom in complex **3** (Figure 2). The extent of bending of the aromatic system is however 0.498 Å, much less than in the platinum complex **3**. Structurally it is remarkable that the N–N distances in the platinum and rhenium complexes are 2.812 and 2.804 Å, respectively, which is significantly larger than that in the parent compound, 2.685 Å. This is readily explained by the strong nitrogen–metal bond of the large transition metal ions. Although the nitrogen–nitrogen distance is larger, this is balanced by a compression in the naphthalene residue. This is evident at the periphery of the naphthalene residue, where the C5–C13 and C5–C5* separation as well as that of C7–C10 and C7–C7* atoms are less than in 4,9-dichloroquino[7,8-*h*]quinoline **1** (Table 1).

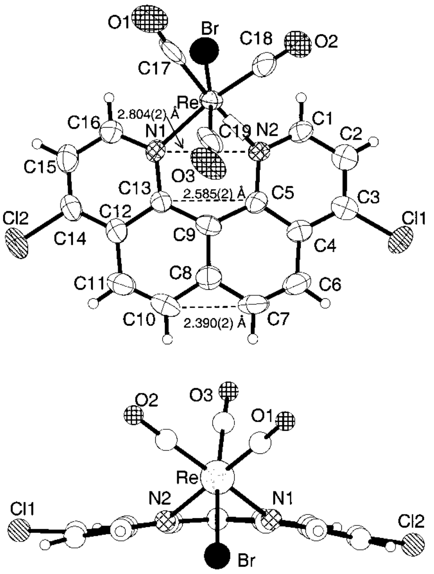

Figure 2. Diamond plot of **5** in front and side view.

Table 1. Important bond lengths of **1** as well as of the metal complexes **3** and **5**.

Compound	N–N [Å]	C5–C13 or C5–C5* [Å]	C7–C10 or C7–C7* [Å]
1	2.685(6)	2.604(6)	2.455(6)
3	2.812	2.481	2.410
5	2.804(2)	2.585(2)	2.390(2)

The unusual thermal and chemical stability of the metal complexes are a consequence of the unique "out-of-plane" position and conformational stabilty of the metal atom in the aromatic system. Thus the Pt complex can be heated to 380 °C for several days without decomposition and it is stable in hot concentrated sulfuric acid.

Moreover, this system is excellent for structure-activity studies in catalysis because the basicity of the chelating nitrogen atoms can be adjusted over a wide range with different substituents at the 4,9-positions without the influence of steric effects.

Structure–activity relationships suggest the use of the platinum-complex **3** as a cytostatic agent.

Experimental Section

1: The ligand 4,9-dichloroquino[7,8-*h*]quinoline was synthesized with modifications of Zirnstein's procedure.[9] The thermal decarboxylation step was performed in small quantities in order to increase the yield. Moreover, the use of of active charcoal RO 0.8 (Aldrich) was important in purification of the ester in the third step. M.p. 236 °C (decomp.); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 7.99$ (d, $^3J = 4.8$ Hz, 2H; 3,10-H), 8.38 (AB, $^3J = 8.9$ Hz, 2H; 6,7-H), 8.54 (AB, $^3J = 8.9$ Hz, 2H; 5,8-H), 9.19 (d, $^3J = 4.8$ Hz, 2H; 2,11-H); IR (KBr): $\tilde{\nu} = 3097$ (w), 3074 (w), 3036 (w), 1626 (m), 1606 (s), 1587 (s), 1541 (m), 1522(m), 1496 (m), 1478 (s), 1409 (s), 1339 (m), 1226 (m), 1013 (s), 840 (s), 769 (s), 691 (s), 681 cm^{-1} (m); MS (EI): *m*/*z* (%): 298 (100, $[M]^+$, isotopic pattern for 2Cl), 263 (29.95, isotopic pattern for 1Cl), 236 (4.19, isotopic pattern for 1Cl), 228 (8.06), 201 (9.33), 174 (4.65), 149 (10.12, $[M]^{2+}$); HR-MS (EI): *m*/*z*: found: 298.00642 ($[M]^+$), calcd.: 298.00645.

3: A solution of **1** (59.8 mg, 0.2 mmol) in 20 mL of dry dichloromethane under argon was added over a 2 h period to a boiling solution of [di-μ-chlorodichlorobis(ethylene)platinum(II)] (58.8 mg, 0.1 mmol). After heating for an additional hour, the solution was filtered to give a clear yellow solution. This solution was reduced in volume and the resultant yellow solid was recrystallized from dichloromethane. Yield: 107.3 mg (91.2%). M.p. > 315 °C; ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 25 °C, TMS): $\delta = 7.84$ (d, $^3J = 6.0$ Hz, 2H; 3,10-H), 8.31 (AB, $^3J = 9.1$ Hz, 2H; 6,7-H), 8.61 (AB, $^3J = 9.1$ Hz, 2H; 5,8-H), 9.66 (d, $^3J = 6.0$ Hz, 2H; 2,11-H); IR (KBr): $\tilde{\nu} = 3123$ (w), 3091 (m), 3060 (m), 3039 (w), 1611 (s), 1575 (s), 1559 (m), 1520 (w), 1478 (s), 1409 (s), 1348 (s), 1221 (s), 1199 (s), 1028 (s), 857 (s), 845 (s), 766 (m), 704 (s), 677 cm^{-1} (m); MS (EI): *m*/*z* (%): 563 (4.98, $[M^+]$, isotopic pattern for 4Cl), 528 (10.24, $[M^+ - \text{Cl}]$, isotopic pattern for Pt$_1$Cl$_3$), 492 (6.18, $[M^+ - \text{H} - 2\,\text{Cl}]$, isotopic pattern for Pt$_1$Cl$_2$), 456 (8.56).

5: A suspension of [bromotetracarbonylrhenium(I)] dimer (75.6 mg, 0.1 mmol) and **1** (59.8 mg, 0.2 mmol) in 50 mL of THF under argon was heated at reflux for 5 days. The solution became red-orange after 2 days and a dark red-orange solid formed after 5 days. The product was filtered under argon, washed with cold THF and dichloromethane, and recrystallized from THF. Yield: 83.7 mg (64.5%). M.p. 288 °C (decomp); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$, 20 °C, TMS): $\delta = 7.81$ (d, $^3J = 5.8$ Hz, 2H; 3,10-H), 8.24 (AB, $^3J = 9.0$ Hz, 2H; 6,7-H), 8.60 (AB, $^3J = 9.0$ Hz, 2H; 5,8-H), 9.73 (d, $^3J = 5.8$ Hz, 2H; 2,11-H); IR (KBr): $\tilde{\nu} = 2962$ (s), 2927 (s), 2854 (m), 2020 (s, ν(C-O)), 1920 (s, ν(C-O)), 1890 (s, ν(C-O)), 1730 (w), 1614 (w), 1577 (w), 1553 (w), 1467 (w), 1023 (s), 864 (m), 843 (m), 701 cm^{-1} (m); MS (EI): *m*/*z* (%): 648 (51.71, $[M^+]$, isotopic pattern for Re$_1$Cl$_2$Br$_1$) 620 (31.18, $[M^+ - \text{CO}]$), 592 (94.95, $[M^+ - 2\,\text{CO}]$), 564 (28.06, $[M^+ - 3\,\text{CO}]$); HR-MS (EI): *m*/*z*: found: 647.866, calcd.: 647.8655.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-164921 (**3**) and CCDC-164920 (**5**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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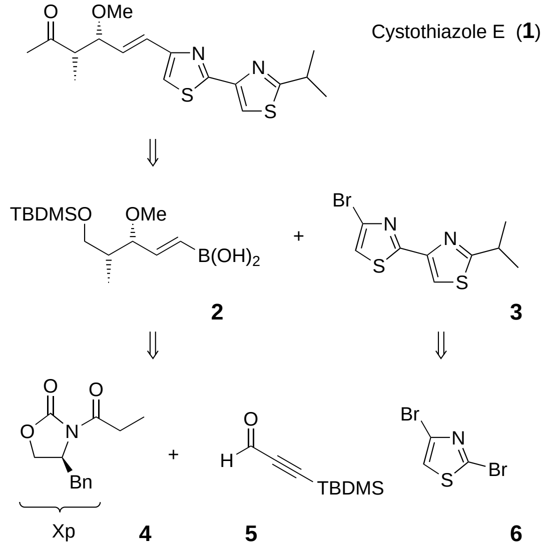
Regioselective Cross-Coupling Reactions as an Entry into Biologically Relevant Bithiazoles: First Total Synthesis of Cystothiazole E**

Thorsten Bach* and Stefan Heuser

Dedicated to Professor Rolf Gleiter
on the occasion of his 65th birthday

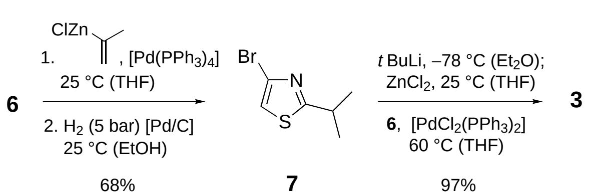
2′,4-Disubstituted 2,4′-bithiazoles are incorporated in several biologically relevant natural products which exhibit anti-infective and cytotoxic properties.[1] In previous syntheses access to the heterocyclic bithiazole core was based exclusively on the classical Hantzsch thiazole methodology.[2] Because of their regioselectivity[3] Pd-catalyzed cross-coupling reactions[4] of 2,4-dibromothiazole[5] appeared to offer an alternative shorter entry into bithiazoles which would allow a great variability in the choice of substituents at the 2′- and 4-positions. Herein we report the application of this strategy to the total synthesis of cystothiazole E (**1**).

The bithiazole **1** and several structurally related products were isolated by Sakagami et al. from a culture broth of the myxobacterium *Cystobacter fuscus* AJ-13278.[1a] The absolute and relative configuration of the stereogenic centers of **1** could not be determined. In analogy to related bithiazoles a *syn*-arrangement of the methyl and the methoxy group was likely. Following the above-mentioned concept we envisioned a Suzuki cross-coupling[6] of the building blocks **2** and **3** as a possible key step for the construction of the carbon skeleton of **1** (Scheme 1). While the vinyl boronic acid **2** was to be derived from the fragements **4** and **5** by a stereoselective aldol reaction,[7] the synthesis of bithiazole **3** was planned starting from 2,4-dibromothiazole (**6**).



Scheme 1. Retrosynthetic disconnection of the target molecule cystothiazole E (**1**); TBDMS = *tert*-butyldimethylsilyl.

Initial attempts aimed at a cross-coupling of isopropyl zinc chloride with 2,4-dibromothiazole (**6**) were not promising and delivered only minor quantities of the desired product **7**. In contrast, isopropenyl zinc chloride reacted smoothly (96% yield, Scheme 2). The subsequent hydrogenation proceeded slowly at atmospheric pressure. At elevated pressure (5 bar) the conversion went to completion, however, the product is prone to hydrodebromination under these conditions and a prolonged hydrogenation should be avoided. The 4-bromothiazole **7** was converted into a carbon nucleophile by a halogen–metal exchange reaction.[8] After transmetalation with zinc chloride the aryl metal compound reacted regioselectively with **6** to afford the desired intermediate **3** (Scheme 2).



Scheme 2. Synthesis of the bithiazole building block **3** by a regioselective cross-coupling.

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