



## 'Melen complexes': a new family of Schiff base metal chelates derived from di-Meldrum's acid derivatives

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### ABSTRACT

A new family of  $N_2O_2$ -tetradentate ligands and complexes derived thereof, based on Meldrum's acid and diamines, has been developed. The structure of **7b** has been unequivocally established by an X-ray crystallographic study. The general strategy has been successfully applied to the synthesis of a tridentate ligand that when reacted with  $Et_2Zn$  resulted in the formation of a coordinatively linked dimer.

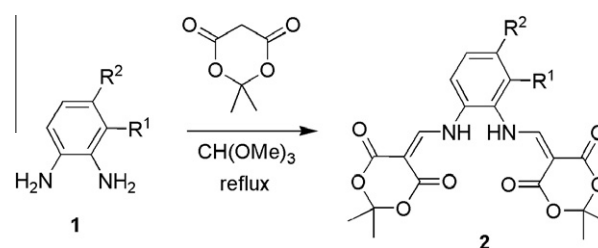
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Since their discovery in the 1860s,<sup>1</sup> Schiff base (SB) complexes continue to play an important role in the development of main group and transition metal coordination chemistry.<sup>2</sup> This is due to their preparative accessibility, diversity, and structural variability and to the fact that, in particular those with  $N_2O_2$ -tetradentate ligands have been recognized as useful models for metallobiosites. The most important early contribution, with respect to the latter, was provided by Jacobsen<sup>3</sup> and Katsuki<sup>4</sup> in the early 1990s, who extended the principles of cytochrome P-450 reactivity to the asymmetric epoxidation of unfunctionalized olefins using homo-chiral salen-type manganese(III) SB catalysts. Since then, there has been a resurgence of interest in chiral salen-type ligands as scaffolds for asymmetric catalysis and many second-generation salen-complexes for oxo transfer<sup>5</sup> and other reactions<sup>6</sup> have been developed.

It is well-known in homogeneous asymmetric catalysis that although sterics play the major role in the asymmetric induction mechanism, electronic effects have also been shown to be quite important.<sup>7</sup> However, of the many effective chiral ligands, only a few are synthetically or structurally well-suited to electronic tuning and hence optimization. Therefore, the ability to easily synthesize a series of structurally similar ligands with subtle steric and electronic variations is highly desirable. Meldrum's acid is an easily prepared and versatile reagent<sup>8</sup> which is more acidic than acyclic malonate esters, due to better  $\pi$ -orbital overlap of the resultant anion within the cyclic structure,<sup>9</sup> and as such potentially useful for the development of novel metal-chelating agents. The synthesis of *o*-phenylenediamine-bis(methylene Meldrum's acid) derivatives (Scheme 1) was co-developed and reported by the main author in 2002 for the elaboration of 1,10-phenanthrolines.<sup>10</sup> The above considerations, in addition to the topological similarity between these systems and salen-type SB ligands prompted us to study their metal-chelating properties. Thus, herein we now report a new

family of  $N_2O_2$ -tetradentate Schiff base complexes derived from Meldrum's acid and *o*-phenylene-diamines. In addition, we show that through reaction with aliphatic 1,2-diamines, chiral-tetradentate, and tridentate ligands and metal complexes derived thereof can be obtained for which an example of each is given. By analogy with salen-complexes, we have termed this new family of metal chelates 'melen-complexes'.

Thus, a series of novel and known di-Meldrum's acid derivatives **2a–g** were conveniently prepared by refluxing *o*-phenylene diamines **1a–g** with 2 equiv of 5-methoxymethylene Meldrum's acid<sup>11</sup> (generated in situ) in trimethyl orthoformate (Table 1). At this stage,



Scheme 1.

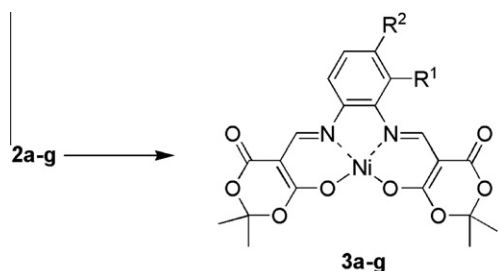
Table 1

Synthesis of di-Meldrum's acid derivatives from *o*-phenylene diamines according to Scheme 1

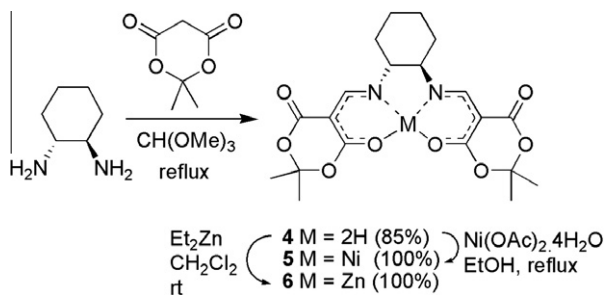
Entry	Diamine	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%)
1	<b>1a</b>	H	H	<b>2a</b> <sup>10</sup>	70
2	<b>1b</b>	H	Me	<b>2b</b> <sup>10</sup>	82
3	<b>1c</b>	H	NO <sub>2</sub>	<b>2c</b>	42
4	<b>1d</b>	H	Cl	<b>2d</b> <sup>10</sup>	34
5	<b>1e</b>	H	OMe	<b>2e</b>	35
6	<b>1f</b>	Me	H	<b>2f</b>	84
7	<b>1g</b>	NO <sub>2</sub>	H	<b>2g</b>	39

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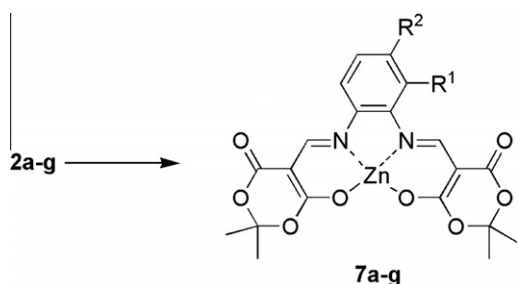
E-mail address: [amontalban@arenapharm.com](mailto:amontalban@arenapharm.com) (A.G. Montalban).



Scheme 2.

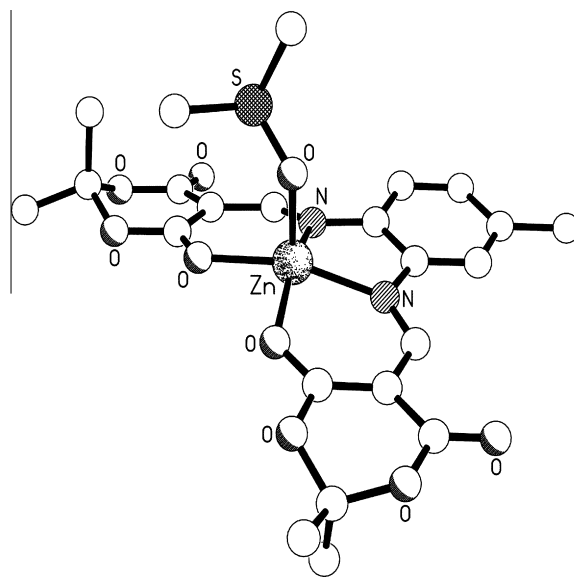


Scheme 3.



Scheme 4.

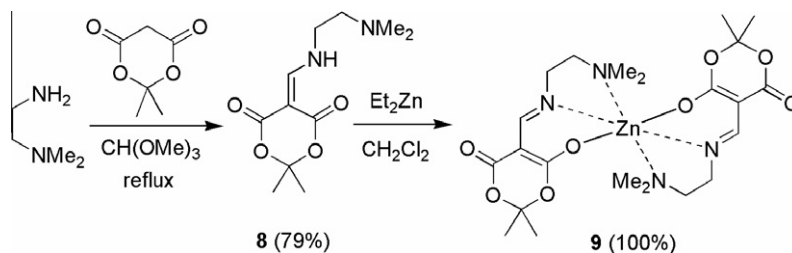
no attempts were made to further optimize the reaction conditions. In the case of **2e**, however, 2 equiv of triethylamine were added to the reaction mixture in order to neutralize the commercially available dihydrochloride salt of **1e**.<sup>12</sup> With the requisite N<sub>2</sub>O<sub>2</sub>-tetradentate ligands in hand, next, we turned our attention to explore their metal-coordinating properties. To simplify the characterization, we decided to start with the synthesis of diamagnetic d<sup>8</sup> Ni(II)-complexes which we rendered suitable due to the cation size and preferred coordination geometry (square planar). Indeed, when di-Meldrum's acid derivatives **2a–g** were treated with 1 equiv of Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O in refluxing ethanol, the novel SB complexes **3a–g** were formed quantitatively (Scheme 2). The initial suspensions

Figure 1. The molecular structure of **7b**.

cleared and turned orange after 30 min. After reflux for 3 h, the solvent was rotary evaporated and the red–orange solids obtained were dried under vacuum. All spectroscopic data<sup>13</sup> were consistent with the proposed structures except for complexes **3f** and **g** that resisted adequate characterization due to solubility issues. Similarly, reaction of (*R,R*)-1,2-diaminocyclohexane with Meldrum's acid (vide supra) followed by treatment of the intermediate chiral N<sub>2</sub>O<sub>2</sub>-tetradentate ligand **4** with Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O in refluxing ethanol resulted again in the quantitative formation of complex **5** as a red solid (Scheme 3).<sup>14</sup> On the other hand, the same reaction, but with Zn(OAc)<sub>2</sub>·2H<sub>2</sub>O instead, was not as efficient. However, when **4** was treated with 1 equiv of Et<sub>2</sub>Zn<sup>15</sup> (1.0 M solution in hexane) at ambient temperature in dichloromethane, the corresponding zinc-complex **6** was obtained quantitatively (Scheme 3). The analogous reaction of **2a–g** with Et<sub>2</sub>Zn resulted in the quantitative formation of metal chelates **7a–g** (Scheme 4).

In contrast, to compounds **3f** and **g**, the corresponding Zn-complexes **7f** and **g** were soluble enough to allow adequate characterization.<sup>16</sup> In addition, crystals of complex **7b** suitable for X-ray crystallography were obtained from DMSO.<sup>17</sup> The structure of **7b** (Fig. 1) shows the zinc to have adopted a square pyramidal coordination geometry with the DMSO oxygen atom occupying the apical site; the metal lies ca. 0.41 Å out of the N<sub>2</sub>O<sub>2</sub> basal plane which is coplanar to better than 0.01 Å.

Finally, the strategy was applied to the synthesis of a tridentate Meldrum's acid derivative (Scheme 5). Thus, reaction of *N,N*-dimethylethane-1,2-diamine with Meldrum's acid under the above general conditions gave the desired tridentate ligand **8** in 79% yield (Scheme 5).



Scheme 5.

Subsequent treatment of **8** with 0.5 equiv of Et<sub>2</sub>Zn in dichloromethane at ambient temperature gave complex **9** as a pale yellow solid in quantitative yield (Scheme 5). Both, NMR- and high resolution MS-data were consistent with the proposed dimer structure.<sup>18</sup> Interestingly, reaction of **8** with Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O under the above conditions resulted only in recovery of the starting material.

In summary, we have developed a new family of N<sub>2</sub>O<sub>2</sub>-tetradentate ligands and complexes derived thereof by combining Meldrum's acid with a variety of diamines. By analogy with salen-complexes, and due to the ease of synthesis and suitability to electronic tuning, melen-complexes should have rich and varied catalytic activities. Such properties are currently being investigated and will be reported in due course.

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12. *Synthetic procedure for the preparation of di-Meldrum's acid derivative 2e*: The general procedure was followed except that 2 equiv of Et<sub>3</sub>N was added to the reaction mixture. Thus, Meldrum's acid (0.68 g, 4.72 mmol) was gently refluxed in CH(OMe)<sub>3</sub> (6.8 mL) for 2 h. After this time, the dihydrochloride salt of diamine **1e** (0.50 g, 2.36 mmol) was added followed by Et<sub>3</sub>N (2 equiv, 0.66 mL) and the resulting mixture further refluxed for 2 h. The reaction mixture was allowed to cool, the solvent rotary evaporated and the residue was re-dissolved in EtOAc (50 mL). The organic layer was washed with H<sub>2</sub>O (3 × 50 mL), dried (MgSO<sub>4</sub>) and rotary evaporated. The residue was triturated with Et<sub>2</sub>O and filtered to give **2e** (0.37 g, 35%) after drying as an off-white solid.
13. *Selected data for complexes 3c and d*: (**3c**) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.73 (s, 12H), 7.64 (d, J = 9.0 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.42 (s, 1H), 8.83 (s, 2H). (**3d**) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.71 (s, 12H), 7.12 (dd, J = 1.8 and 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 8.22 (s, 2H).
14. *Selected data for ligand 4*: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.44 (t, J = 9.9 Hz, 2H), 1.65 (s, 6H), 1.67 (s, 6H), 1.73 (d, J = 9.1 Hz, 2H), 1.93 (d, J = 8.6 Hz, 2H), 2.22 (d, J = 13.4 Hz, 2H), 3.42–3.48 (m, 2H), 8.07 (d, J = 14.5 Hz, 2H), 9.60 (dd, J = 7.2 and 14.5 Hz, 2H). HRMS (FAB) calcd for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>: [M<sup>+</sup>] 422.1689, found [M<sup>+</sup>] 422.1683. [α]<sub>D</sub><sup>20</sup>: –179.5 (c 2, CHCl<sub>3</sub>).
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16. *Selected data for Zn-complex 7g*: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) 1.70 (s, 12H), 7.20 (d, J = 9.0 Hz, 1H), 7.33 (t, J = 9.0 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 8.21 (s, 1H), 8.88 (s, 1H). HRMS (FAB) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>10</sub>Zn: [M<sup>+</sup>] 524.0284, found [M<sup>+</sup>] 524.0269.
17. *Crystal data for 7b*: C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>9</sub>SZn, M = 571.89, triclinic, P $\bar{1}$  (no. 2), a = 9.3283(12), b = 12.4948(16), c = 13.1171(17) Å, α = 61.859(9), β = 78.736(10), γ = 69.129(9)°, V = 1259.0(3) Å<sup>3</sup>, Z = 2, D<sub>c</sub> = 1.509 g cm<sup>-3</sup>, μ(MoKα) = 1.113 mm<sup>-1</sup>, T = 293 K, yellow diamond prisms, Siemens P4 diffractometer; 4258 independent measured reflections (R<sub>int</sub> = 0.0234), F<sup>2</sup> refinement, R<sub>1</sub>(obs) = 0.0358, wR<sub>2</sub>(all) = 0.0894, 3564 independent observed absorption-corrected reflections [|F<sub>o</sub>| > 4σ(|F<sub>o</sub>|)], 2θ<sub>max</sub> = 50°, 332 parameters. CCDC 773195.
18. *Selected data for complex 9*: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) 1.65 (m, 12H), 2.25 (s, 12H), 2.42–2.58 (m, 2H), 2.67–2.81 (m, 2H), 3.42–3.52 (m, 2H), 3.61–3.69 (m, 2H), 8.54 (s, 2H). HRMS (FAB) calcd for C<sub>22</sub>H<sub>35</sub>N<sub>4</sub>O<sub>8</sub>Zn: [M+H]<sup>+</sup> 547.1746, found [M+H]<sup>+</sup> 547.1716.