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Unprecedented reductive cyclisation of salophen ligands to tetrahydroquinoxalines during metal complex formation†

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The synthesis of novel tetrahydroquinoxalines by a metal induced one-electron reductive cyclisation of salophen ligands was found to occur when a salophen ligand was treated with chromium(II) chloride or decamethylcobaltocene.

Salen and salophen ligands (Fig. 1) are very commonly utilised privileged ligands which readily form mono- and/or poly-metallic complexes with just about any metal in the periodic table.[1] The resulting metal complexes have a wide range of catalytic[2] and other[3] applications. For example; chiral manganese(salen) complexes catalyse the asymmetric epoxidation of alkenes, cobalt(salen) complexes catalyse the ring-opening of epoxides, chiral salen complexes of titanium and vanadium catalyse asymmetric cyanohydrin synthesis and salen and salophen complexes of aluminium catalyse the synthesis of cyclic carbonates and oxazolidinones from carbon dioxide and epoxides or aziridines.[4,5]

Salen and salophen complexes of chromium are also very well-known and widely used catalysts[6] and we have investigated the use of chromium(III)(salophen) complexes as catalysts for cyclic carbonate synthesis from carbon dioxide and both terminal and internal epoxides.[7] In the course of this work we encountered a previously unknown side reaction which complicates the usual preparation of chromium(salophen) complexes by treatment of a salophen ligand with chromium(II) chloride followed by oxidation using atmospheric oxygen. In this paper we report this side reaction for the first time, explore its scope and propose a reaction mechanism.

Treatment of salophen ligand **1a** with chromium(II) chloride gave, in addition to the expected chromium(III)(salophen) chloride complex **2a**, an unexpected side product (Scheme 1). The side product could be isolated in 5% yield as white crystals by column chromatography and its structure was determined to be tetrahydroquinoxaline **3a** by X-ray crystallography (Fig. 2).‡ A key feature of the crystal structure is the presence of two intramolecular hydrogen bonds which result in the formation of a conformation in which the two phenol rings are approximately orthogonal to the plane of the tetrahydroquinoxaline. As a consequence, the hydrogens at position R^4 are each located under the centre of the other phenol ring.

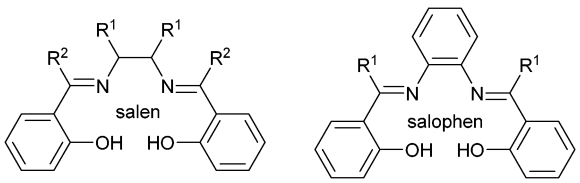

Fig. 1 General structures of salen and salophen ligands. Substituents can also be present on the aromatic rings.

The proton NMR spectrum of compound **3a** in deuterated chloroform suggested that the same conformation was adopted in chloroform solution as the signal for the hydrogen at position R^4 was found to occur at 5.75 ppm consistent with it being shielded due to its location within the sphere of influence associated with the ring current of the other phenol ring.[8] This signal was also found not to be temperature dependent between 218 and 328 K, suggesting that the proton at position R^4 is unable to move out of the sphere of influence associated with the ring current of the other phenol ring throughout this temperature range. This implies that there is no rotation around the CH–phenol bonds and hence that the intramolecular hydrogen bonds are maintained throughout this temperature range.

The formation of tetrahydroquinoxaline **3a** can be explained by the mechanism shown in Scheme 2. Chromium(II) chloride can act as a one electron reductant, forming a highly delocalised radical anion, one resonance form of which is represented by structure **4**. There is literature precedent for the formation of radical anions from salen and salophen complexes.[9] Radical anion **4** can

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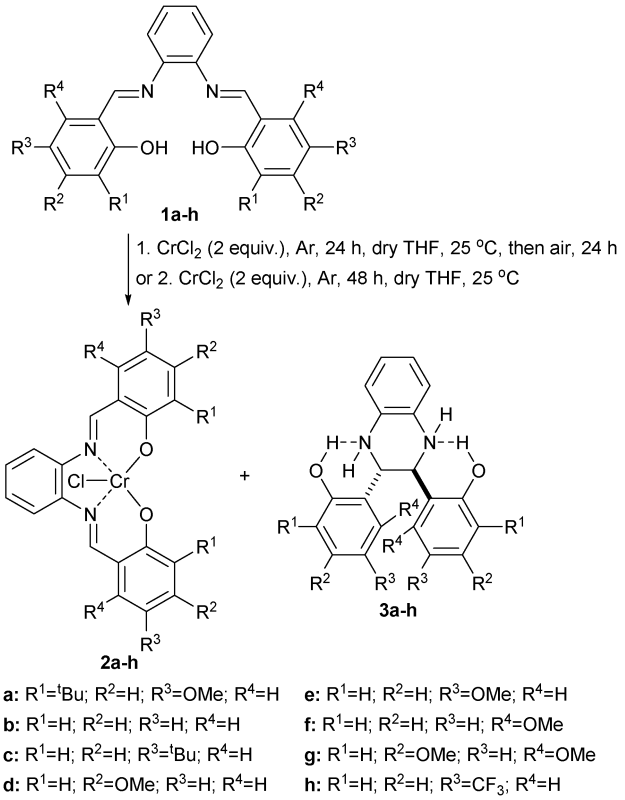
† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for tetrahydroquinoxalines **3a–h**; X-ray data and cyclic voltammograms. CCDC 1983169–1983173. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc01192d



Scheme 1 Synthesis of chromium(III)(salophen) complexes **2a–h** and *trans*-tetrahydroquinoxalines **3a–h**.

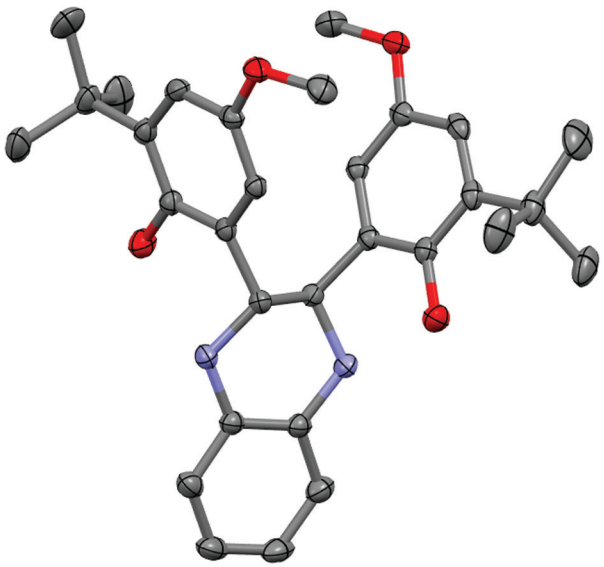
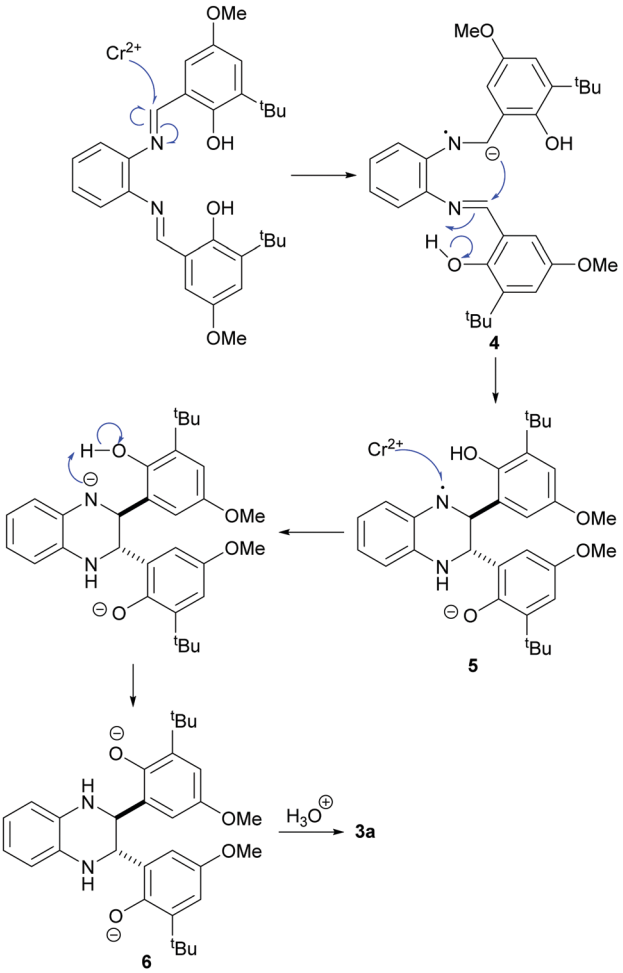


Fig. 2 ORTEP plot of tetrahydroquinoxaline **3a**. Hydrogen atoms have been omitted for clarity and ellipsoids are shown at 50% probability.

then undergo a favourable 6-endo-trig ring closure[10] followed by proton transfer from a phenol to give cyclised radical **5**. A second chromium(II) chloride can then reduce radical **5** to the corresponding anion; which, after proton transfer from the other phenol, would give bis-phenoxide **6**. Protonation of compound **6** during work-up gives tetrahydroquinoxaline **3a**. To confirm that compound



Scheme 2 Proposed mechanism for the formation of tetrahydroquinoxaline **3a**.

3a was formed during the formation of salophen complex **2a** and not as a decomposition product of **2a** during its crystallisation, a batch of **2a** was prepared and the unpurified reaction mixture analysed by high resolution mass spectrometry which showed the presence of both **2a** and **3a**. Formation of tetrahydroquinoxaline **3a** also occurred, in 5% yield, when stirring under air for 24 hours was omitted from the synthetic procedure (Scheme 1, conditions 2). A control experiment in which salophen ligand **1a** was stirred under argon in THF, in the absence of chromium(II) chloride, led only to the recovery of starting material. Treatment of salen ligand (Fig. 1, $R^1 = R^2 = H$) with chromium(II) chloride led only to the corresponding chromium(salen) complex, consistent with formation of a highly delocalised radical anion intermediate being essential for reductive cyclisation.

To investigate the generality of this tetrahydroquinoxaline synthesis, eight salophen ligands (**1a–h**), with different electronic and steric properties were reacted with chromium(II) chloride under conditions 2 used for the synthesis of **3a** (Scheme 1). In each case the corresponding *trans*-tetrahydroquinoxaline **3a–h** was isolated in yields of 2–15% after column chromatography.

Crystals of four additional tetrahydroquinoxalines (**3b, c, f, h**) were grown and analysed by X-ray crystallography.‡ In each

case the X-ray structures confirmed the *trans*-orientation of the phenolic rings and showed the same hydrogen bond stabilised conformation as for compound **3a** (Fig. 2). The intramolecular hydrogen bonds in these structures all had lengths of 1.80–2.08 Å and donor–acceptor distances of 2.65–2.78 Å which are consistent with the formation of moderate intramolecular hydrogen bonds.[11] There is no apparent trend in the yield of compounds **3a–h** as the electronic properties of the salophen ligands were varied. In particular, entries 4, 6 and 8 of Table 1 all gave the same yield of tetrahydroquinoxaline **3** even though two of the substrates (**2d**, **f**) possess electron-donating methoxy groups on their phenol rings whilst the phenol rings of salophen **2h** are substituted with electron withdrawing trifluoromethyl groups. Similarly, there appears to be no influence of sterically demanding *tert*-butyl groups on the salophen ligands (compare entries 1 and 5 and entries 2 and 3). The formation of tetrahydroquinoxaline **3g** was particularly low (Table 1, entry 7), which can be attributed to stability issues as the isolated product slowly decomposed over time.

To investigate the importance of the chromium in tetrahydroquinoxaline formation, electron rich and electron neutral salophen ligands (**1a** and **1b** respectively), were reacted with cobalt(II) chloride instead of chromium(II) chloride under otherwise identical reaction conditions (Scheme 1, conditions 2). No formation of tetrahydroquinoxalines **3a**, **b** was detected by mass spectrometry or NMR analysis of the unpurified reaction mixtures. Therefore, a range of one-electron reducing agents with different redox potentials were screened under the same reaction conditions. The reducing agents used were: decamethylcobaltocene,[12] decamethylferrocene,[13] titanocene dichloride,[14] samarium(II) iodide[15] and tetrathiafulvene.[16] When screened with salophen ligands **1a**, **b**, only decamethylcobaltocene led to the formation of tetrahydroquinoxalines **3a**, **b**, in 10% and 15% yield respectively (Table 1, entries 9 and 10). These yields are approximately double those obtained using chromium(II) chloride which could be attributed both to the difference in reducing potential of the chromium(II) and cobalt(II) species and to the inability of decamethylcobaltocene to act as a cobalt source for the formation of a cobalt(salophen) complex. The formation of tetrahydroquinoxalines **3a**, **b** from ligands **1a**, **b** upon treatment with decamethylcobaltocene proves that the reaction does not occur *via* a chromium(salophen) complex and so must involve cyclisation of the free ligand.

Table 1 Substrate scope

Entry	Product	R^1	R^2	R^3	R^4	Yield[a] (%)
1	**3a**	^{t}Bu	H	OMe	H	5
2	**3b**	H	H	H	H	8
3	**3c**	H	H	^{t}Bu	H	8
4	**3d**	H	OMe	H	H	12
5	**3e**	H	H	OMe	H	5
6	**3f**	H	H	H	OMe	12
7	**3g**	H	OMe	H	OMe	2
8	**3h**	H	H	CF_3	H	12
9[b]	**3a**	^{t}Bu	H	OMe	H	10
10[b]	**3b**	H	H	H	H	15

[a] Isolated yields after purification by column chromatography. [b] Using decamethylcobaltocene as the reducing agent.

Literature data[16–18] suggested that decamethylcobaltocene was the strongest of these reducing agents under standard aqueous electrochemical conditions. To confirm that this was also the case under the anhydrous reaction conditions used for the synthesis of tetrahydroquinoxalines, cyclic voltammetry[18] of all the potential reductants was carried out in anhydrous THF under a nitrogen atmosphere and this confirmed that decamethylcobaltocene was the strongest reducing agent under the reaction conditions (Table 2). However, the nature of the reductant (for example its solubility and stability under the reaction conditions) and the relative rates associated with its ability to act as a reductant and to form a metal(salophen) complex must also have an influence on the reductive cyclisation. This is shown by samarium(II) iodide and titanocene dichloride which have reduction potentials between those of decamethylcobaltocene and chromium(II) chloride and so would be expected to be capable of forming tetrahydroquinoxalines **3**, but failed to do so.

Cyclic voltammetry was also used to investigate whether the reducing agent involved in reactions carried out in the presence of chromium(II) chloride was chromium(II) chloride itself or the chromium(II)(salophen) complex formed *in situ* from chromium(II) chloride and ligand **1a**. Comparison of the cyclic voltammograms of chromium(II) chloride and complex **2a** showed that the chromium(II)(salophen) complex (formed by electrochemical reduction of complex **2a** within the cyclic voltammetry experiment) is a much weaker reducing agent than chromium(II) chloride. As expected, the cyclic voltammogram of complex **2a** did show two reversible, one-electron redox processes, due to sequential oxidation of the phenolates as previously reported for other salen and salophen complexes.[19] This rules out mechanistic pathways which involve a chromium(II)(salophen) species acting as a reducing agent for an uncomplexed salen ligand or the complexed chromium acting as a one-electron reductant for its own salophen ligand to give a chromium(III) complex of the radical anion of a salophen ligand.

This work has shown that the synthesis of metal(salophen) complexes from a salophen ligand and a metal salt is not always as clean a reaction as generally assumed. Care should be taken to purify the resulting metal(salophen) complexes prior to their use as catalysts, especially when the metal is capable of undergoing redox reactions to avoid misleading results.

The synthesis of tetrahydroquinoxalines by reductive cyclisation of salophen ligands represents a new and highly stereocontrolled

Table 2 Reduction potentials ($E_{1/2}$) relative to a standard hydrogen electrode (SHE)

One-electron reductant	$E_{1/2}$[a]	$E_{1/2}$[b] (lit)
Decamethylcobaltocene	−1.50	−1.54[20]
Samarium(II) iodide	−1.31	−1.55[21]
Titanocene dichloride	−0.94	−0.81[18]
Chromium(II) chloride	−0.40	−0.41[18]
Decamethylferrocene	−0.16	−0.19[20]
2a	+0.65 and +0.92	na

[a] Measured in dry THF under a nitrogen atmosphere *vs.* a Pt reference electrode. Values were converted to *vs.* SHE (see ESI). [b] Measured under standard electrochemical conditions in aqueous solution.

approach to the synthesis of this heterocyclic ring system which is found in many bioactive molecules including: cholesteryl ester transfer protein inhibitors, prostaglandin D2 receptor antagonists B, M2 acetylcholine receptor agonists, cholesteryl ester transfer protein inhibitors and drugs used for HIV infection treatment.[20]

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Conflicts of interest

There are no conflicts of interest to declare.

Notes and references

‡ X-ray data for compounds **3h, f, b, c and a** have been deposited with CCDC with codes 1983169–1983173 respectively.†

1 *Privileged Chiral Ligands and Catalysts*, ed. Q.-L. Zhou, Wiley-VCH, Weinheim, 2011, ch. 7.
2 K. C. Gupta and A. K. Sutar, *Coord. Chem. Rev.*, 2008, **252**, 1420–1450; R. M. Haak, S. J. Wezenberg and A. W. Kleij, *Chem. Commun.*, 2010, **46**, 2713–2723; A. Zulauf, M. Mellah, X. Hong and E. Schulz, *Dalton Trans.*, 2010, **39**, 6911–6935; S. Matsunaga and M. Shibasaki, *Synthesis*, 2013, 421–437; S. Matsunaga and M. Shibasaki, *Chem. Commun.*, 2014, **50**, 1044–1057; R. Irie, T. Uchida and K. Matsumoto, *Chem. Lett.*, 2015, **44**, 1268–1283; S. Shaw and J. D. White, *Chem. Rev.*, 2019, **119**, 9381–9426; M. Abd El Sater, N. Jaber and E. Schulz, *ChemCatChem*, 2019, **11**, 3662–3687.
3 S. J. Wezenberg and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2008, **47**, 2354–2364; S. Akine and T. Nabeshima, *Dalton Trans.*, 2009, 10395–10408; A. D. Cort, P. De Bernardin, G. Forte and F. Y. Mihan, *Chem. Soc. Rev.*, 2010, **39**, 3863–3874; M. Andruh, *Chem. Commun.*, 2011, **47**, 3025–3042; S. Akine, *J. Inclusion Phenom. Macrocyclic. Chem.*, 2012, **72**, 25–54; C. J. Whiteoak, G. Salassa and A. W. Kleij, *Chem. Soc. Rev.*, 2012, **41**, 622–631; R. M. Clarke and T. Storr, *Dalton Trans.*, 2014, **43**, 9380–9391; A. Erxleben, *Inorg. Chim. Acta*, 2018, **472**, 40–57; G. Yuan, H. Jiang, L. Zhang, Y. Liu and Y. Cui, *Coord. Chem. Rev.*, 2019, **378**, 483–499.
4 P. A. Carvalho, J. W. Comerford, K. J. Lamb, M. North and P. S. Reiss, *Adv. Synth. Catal.*, 2019, **361**, 345–354.
5 M. Sengoden, M. North and A. C. Whitwood, *ChemSusChem*, 2019, **12**, 3296–3303.
6 E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421–431; D. E. Bergbreiter, C. Hobbs and C. Hongfa, *J. Org. Chem.*, 2011, **76**, 523–533; R. Tak, M. Kumar, T. Menapara, M. K. Choudhary, R. I. Kureshy and N. H. Khan, *ChemCatChem*, 2017, **9**, 322–328; S. Bai, B. Li, J. Peng, X. Zhang, Q. Yang and C. Li, *Chem. Sci.*, 2012, **3**, 2864–2867.
7 J. A. Castro-Osma, K. J. Lamb and M. North, *ACS Catal.*, 2016, **6**, 5012–5025.
8 *Structure Elucidation by NMR in Organic Chemistry*, ed. E. Breitmaier, Wiley, Chichester, 1993, pp. 59–60.
9 S. De Angelis, E. Solari, E. Gallo, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *Inorg. Chem.*, 1996, **35**, 5995–6003; J. A. Miranda, C. J. Wade and R. D. Little, *J. Org. Chem.*, 2005, **70**, 8017–8026; M. A. Ischay, M. S. Mubarak and D. G. Peters, *J. Org. Chem.*, 2006, **71**, 623–628.
10 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734–736.
11 *An Introduction to Hydrogen Bonding*, ed. G. A. Jeffrey, Oxford University Press, New York, 1997.
12 W. E. Geiger, *J. Am. Chem. Soc.*, 1974, **96**, 2632–2634.
13 S. Sachdev, R. Maugi, J. Woolley, C. Kirk, Z. Zhou, S. D. R. Christie and M. Platt, *Langmuir*, 2017, **33**, 5464–5472.
14 A. Chaloyard, A. Dormond, J. Tirouflet and N. E. Murr, *J. Chem. Soc., Chem. Commun.*, 1980, 214–216; N. Elmurr, A. Chaloyard and J. Tirouflet, *J. Chem. Soc., Chem. Commun.*, 1980, 446–448.
15 Y. W. Zhong, Y. Z. Dong, K. Fang, K. Izumi, M. H. Xu and G. Q. Lin, *J. Am. Chem. Soc.*, 2005, **127**, 11956–11957.
16 C. Lampard, J. A. Murphy and N. Lewis, *J. Chem. Soc., Chem. Commun.*, 1993, 295–297.
17 N. G. Connelly and W. E. Geiger, *Chem. Rev.*, 1996, **96**, 877–910.
18 P. Vanýsek, *Electrochemical Series* in Handbook of Chemistry and Physics, ed. W. M. Haynes, CRC Press, London, UK, 93rd edn, 2012, ch. 5, pp. 80–90.
19 R. C. Pratt and T. D. P. Stack, *J. Am. Chem. Soc.*, 2003, **125**, 8716–8717; F. Thomas, O. Jarjayes, C. Duboc, C. Philouze, E. Saint-Aman and J. L. Pierre, *Dalton Trans.*, 2004, 2662–2669.
20 M. K. Ghorai, A. K. Sahoo and S. Kumar, *Org. Lett.*, 2011, **13**, 5972–5975; G. D. Xu, G. Q. Yang, Y. Wang, P. L. Shao, J. N. N. Yau, B. Liu, Y. B. Zhao, Y. Sun, X. X. Xie, S. Wang, Y. Zhang, L. X. Xia and Y. Zhao, *Angew. Chem., Int. Ed.*, 2019, **58**, 14082–14088; R. Y. Huang, X. K. Chen, C. L. Mou, G. Y. Luo, Y. J. Li, X. Y. Li, W. Xue, Z. C. Jin and Y. R. Chi, *Org. Lett.*, 2019, **21**, 4340–4344; X. Zhang, J. C. Chen, R. Khan, G. L. Shen, Z. X. He, Y. Y. Zhou and B. M. Fan, *Org. Biomol. Chem.*, 2019, **17**, 10142–10147.

