Convenient Syntheses, based on Cyclohexene Oxide, of Ligands that are Highly Preorganised for Metal Ion Size-based Selectivity

Alvaro S. de Sousa and Robert D. Hancock*

Centre for Molecular Design, University of the Witwatersrand, WITS 2050, Johannesburg, South Africa

Cyclohexene oxide reacts with strong diastereoselectivity with polyamines to give good yields of well defined crystalline products where only one, or sometimes two, pendant groups are present, such as *N*-(2-hydroxycyclohexyl)cyclen or DL-1,7-bis(2-hydroxycyclohexyl)-1,4,7-triazaheptane, which as ligands show strong and predictable preferences for smaller metal ions.

Selective complexation of metal ions for biomedical applications is currently of major scientific interest.[1,2] An important example is the synthesis of ligands for complexation of Gd^{3+} in MRI (magnetic resonance imaging).[3] Such ligands should preferably give complexes with Gd^{3+} which are neutral overall. When based on cyclen (1,4,7,10-tetraazacyclododecane) this requires addition of a single neutral pendent donor group such as a 2-hydroxypropyl or an acetamide group, in addition to the three acetates usually added. To effect monosubstitution of cyclen requires extra synthetic steps for protection of the other three nitrogens.[4] We have found that the cyclohexenyl group reacts in reasonable yield with cyclen to give a single substitution product with only one pandant group, even in the presence of a large excess of cyclohexene oxide. Further, reaction of cyclohexene oxide with diamines and triamines, Fig. 1, yields single substitution products that are crystalline, and consist of only a single enantiomeric pair, instead of the several expected diastereomeric pairs. It seems probable that the first cyclohexenyl group added, which can hydrogen bond with the second addition site *via* its hydroxy group, directs the addition of the second cyclohexenyl group. The syntheses typically involve refluxing amine (1–2 g) in 60 ml anhydrous ethanol with a 4 : 1 stoichiometric excess of cyclohexene oxide for 12 h, after which removal of the solvent under reduced pressure yields a colourless oil that crystallizes on standing.

The cyclohexenyl group promotes selectivity for smaller metal ions when compared to the effect of a simple 2-hydroxyethyl group, which promotes selectivity for large metal ions.[5]

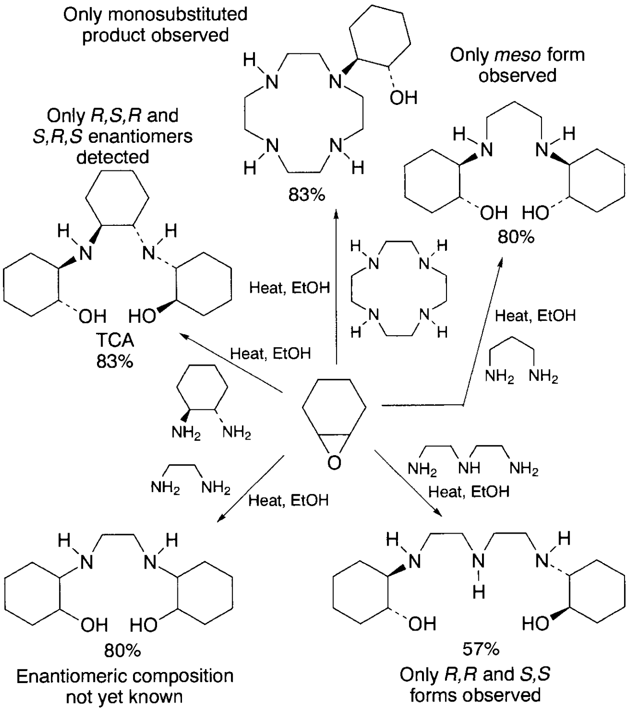


Fig. 1 Synthesis of ligands by means of reaction of polyamines with cyclohexene oxide. The reported yields are non-optimized, and are of

Table 1 shows the protonation constants and formation constants of *N,N'*-bis(2-hydroxycyclohexyl)cyclohexane-1,2-diamine (TCA), compared with those of *N,N'*-(2-hydroxyethyl)ethylenediamine (DHEEN). The cyclohexenyl bridges of TCA cause an increase in log K_1 for the small Cu^{2+} ion (ionic radius 57 pm[6]), and a decrease in log K_1 for the large Pb^{2+} ion (ionic radius 118 pm), compared to DHEEN with its simple ethylene bridges. An interesting aspect of the enhanced stability of the complexes of TCA is the greater acidity of the coordinated hydroxy group of the TCA complexes, as illustrated by the complex with Cu^{II}, eqns. (1), (2).

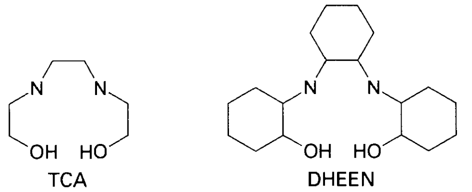
$$[Cu(TCA)]^{2+} + OH^- \rightleftharpoons [Cu(TCA)H_{-1}],\ \log K = 9.26 \quad (1)$$

$$[Cu(DHEEN)]^{2+} + OH^- \rightleftharpoons [Cu(DHEEN)H_{-1}],\ \log K = 6.63 \quad (2)$$

(Calculated assuming pK_w = 13.78 from ref. 7).

The cause of the size-selective behaviour found when ethylene bridges are replaced with cyclohexenyl bridges seems to be the greater curvature of the ligand when it is coordinated to a small metal ion, which relieves steric crowding on the outer side of the ligand caused by the bulky cyclohexenyl bridge. Relief of steric crowding is probably also responsible for the greater acidtiy of the coordinated hydroxy groups where cyclohexenyl bridges are present. The results presented here show the utility of cyclohexene oxide in ligand synthesis, particularly in the strong diastereoselectivity of substitution observed in the products. Ligands produced by substitution with cyclohexenyl oxide present a synthetically simple method of synthesizing novel ligands with useful and interesting metal ion size-based selectivity.

Table 1 Protonation and formation constants of TCA compared to DHEEN, showing the effect of the cyclohexenyl bridges on complex stability of metal ions, and the relation of this effect to size of metal ion



	Ionic radius[b]	DHEEN[a]	TCA
pK_1	—	9.24	9.54
pK_2	—	6.26	4.52
log K_1 Cu^{2+}	57	9.68	11.5
Ni^{2+}	69	6.67	6.84
Zn^{2+}	74	4.79	4.77
Cd^{2+}	95	5.07	4.08
Pb^{2+}	118	6.12	4.8

[a] Formation constants for DHEEN complexes from ref. 7. Formation constants for TCA, this work, 0.1 mol dm^{-3} $NaNO_3$ and 25 °C, determined spectroscopically. [b] Effective ionic radii (pm) from ref. 6. In accord with previous work,[1] ionic radii are given for coordination number six. An exception is for Cu^{II} which is usually square planar with a coordination number of four, so that an ionic radius for coordination number four is

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References

1 R. D. Hancock and A. E. Martell, *Chem. Rev.*, 1989, **89**, 1875.
2 S. Jurisson, D. Berning, W. Jia and D. Ma, *Chem. Rev.*, 1993, **93**, 1137; P. J. Sadler, *Adv. Inorg. Chem.*, 1991, **36**, 1.
3 R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901.
4 K. Pulukkody, T. J. Norman, D. Parker, L. Royle and J. Broan, *J. Chem. Soc., Perkin Trans. 2*, 1993, 605; M. Murru, D. Parker, G. Williams and A. Beeby, *J. Chem. Soc., Chem. Commun.*, 1993, 1116; D. Parker, K. Pulukkody, T. J. Norman, A. Harrison and L. Royle, *J. Chem. Soc., Chem. Commun.*, 1992, 1441.
5 R. D. Hancock, in *Perspectives in Inorganic Chemistry*, ed. A. P. Williams, C. Floriani and A. E. Merbach, Verlag Helv. Chim. Acta, Basel and VCH Weinheim, 1992, pp. 129–151.
6 R. D. Shannon, *Acta Crystallogr., Sect. A*, 1976, **32**, 751.
7 A. E. Martell and R. M. Smith, *Critical Stability Constants*, Plenum, NY, vol. **1–6**, 1974–1977, 1982, 1989.