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Novel C_2 Chiral Diamine Ligands Derived from Cyclic Tröger Bases

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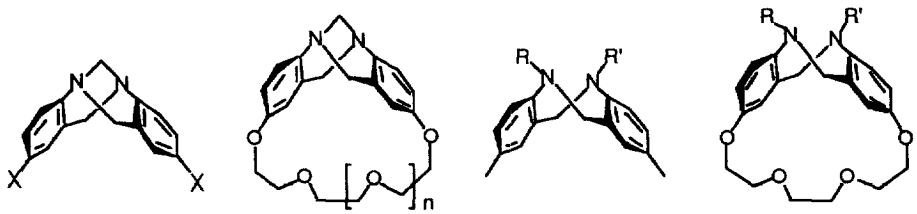
Abstract: The endomethylene bridge in a macrocyclic Tröger base was removed efficiently to provide a dibenzodiazocine derivative, and its *N*-methyl and *N,N'*-dimethyl derivatives. These C_2 chiral diamines could be separated into their optical antipodes by HPLC using a chiral column. Complex formation of these new type ligands with several metal salts was also examined.

Because of its rigid folded structure with C_2 chirality, the readily available Tröger base (**1a**)[1] has attracted many researchers in host-guest chemistry for use as building blocks of acyclic[2] and cyclic[3] host molecules for selective inclusion of chiral guests. Although several macrocyclic Tröger bases, [n.n]trögerophane (n=1-3)[4] and tetraoxa[10]trögerophane (**2a**) as well as pentaoxa[13]trögerophane (**2b**)[5], have been synthesized in our laboratory along this line, the cavity sizes turned out to be rather small for inclusion of organic molecules.



1a (X=Me)
1b (X=OMe)

2a (n=1), **2b** (n=2),
2c (n=3), **2d** (n=4),
2e (n=5)

3a (R=R'=H)
3b (R=Me, R'=H)
3c (R=R'=Me)

4a (R=R'=H)
4b (R=Me, R'=H)
4c (R=R'=Me)

In view of the high yields of such complex molecules obtained from simple one-step cyclizations (**2a**: 46%, **2b**: 34%), we turned our attention from the aromatic concave of **1a** to the outer nitrogen atoms as coordinating sites. Actually **1a** has found use as a chiral modifier of a Pt catalyst[6] and chiral catalysts after complexation at its nitrogens with Rh and Ir salts.[7] We thought removal of the endomethylene in the trögerophanes would make better ligands, because a variety of metal complexes have already reported for the dibenzodiazocine **3a** and its *N*-methyl derivative **3b**.[8]

It should be remembered that the chirality of the open chain **1a** is originated from fixation of configuration around the nitrogens. As a consequence, the lability of the endomethylene group under acidic conditions poses a serious problem of racemization[9] as already recognized by Prelog and Wieland in their monumental work on optical resolution of **1a**.[10] By contrast, the polyether tether in our cyclophane systems was expected to be short enough to prevent such inversion processes even if the endomethylene bridge was removed. Here we report that optical separation of the endomethylene-depleted **4a-c** could actually be achieved by HPLC using a chiral column.

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In this paper we are mainly concerned with the derivatives of **2a**, because it is the smallest monomeric [n]trögerophane obtainable in the polyether series and its tether is of the right length to join the 2,8-positions of the Tröger base unit.[5,11] Removal of the endomethylene bridge could be effected with or without concomitant methylation on the nitrogen(s) as follows.

When **2a** in dioxane was treated with dimethyl sulfate in the presence of sodium hydroxide at room temperature, the *N,N'*-dimethyl compound **4c** was obtained as pale yellow crystals (mp 87.5-88 °C) in 92% yield. It should be noted that the methylation of **1a** was incomplete (ca. 1:1 mixture of **3b** and **3c**) under similar reaction conditions,[12] possibly due to the conformational difference between the intermediate **4b** with a folded geometry and the preferred twisted conformation of the open chain **3b**.[13]

If the intermediate *N*-methylated ammonium salt of **2a** in the above reaction was isolated and hydrolyzed in an alkaline solution, *N*-methyl compound **4b** was obtained as pale yellow crystals (mp 91-92 °C) in 96% yield.

On the other hand, *N*-unsubstituted **4a** was not readily accessible. The nitrosation-CuCl reduction sequence, which has been usually used for **1a** and related compounds[14], failed, since nitrosation of **2a** as well as its open chain analog **1b** resulted in intractable products due to the presence of the electron-rich ether groups. *N*-Benzylation, followed by hydrogenolysis over a Pd catalyst,[15] gave the desired disecondary amine **4a** as colorless crystals (mp 172-172.5 °C), but the yield was poor (13%). Acetylation and benzoylation of **2a** proceeded smoothly providing the corresponding diamides, but the subsequent hydrolysis was very sluggish. In contrast, although trifluoroacetylation of **2a** in trifluoroacetic anhydride required longer reaction times (65 h), the product, not a bis(trifluoroacetamide), but a trifluoroacetamide trifluoroacetate salt [mp 150-151.5 °C (dec)] obtained in 79% yield, was readily hydrolyzed in refluxing MeOH in the presence of K_2CO_3 to provide **4a** in 79%.

Although attempts at optical resolution by salt formation with chiral acids were so far unsuccessful, complete HPLC separation could be achieved by means of an optically active column. The most efficient proved to be a Chiralcel OJ column (cellulose *p*-methylbenzoate-coated silica gel)[16] and as shown in Figure 1, remarkable separation was achieved for **4a** with separation factor (α) of 6.5 and resolution (Rs) of 10.0. The efficiency of separation decreased in the order: **4a** > **2a** > **4b** > **4c**, but still baseline separation was obtained for **4c**. Therefore, semipreparative separations were readily made for **2a** and **4a**.[17] It is interesting to note that while both methacrylate-based Chiralpak OP and cellulose-based Chiralcel OJ were equally effective for the open chain **1a** and **1b**, the former showed no separation for **2a**, probably reflecting the difference in recognition sites.

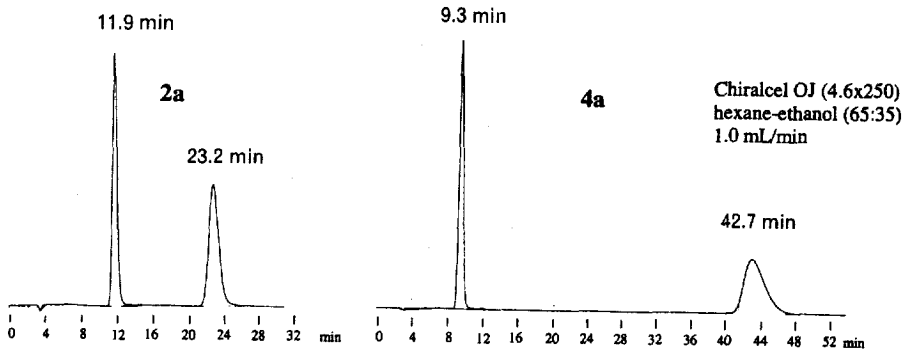

Figure 1. HPLC separation of optical isomers of **2a** and **4a**.

Preliminary complexation studies showed that the diamines **4a-c**, though as racemic compounds, were good ligands for metal salts in the same way as the open chain **3a** and **3b**.[8] For example, $(\mathbf{4a})_2$•$NiCl_2$ complex was readily obtained as orange crystals, the X-ray structure of which is as shown in Figure 2.[18] In view of a number of asymmetric reactions utilizing chiral diamine ligands for organometallic compounds,[19] we examined complexation of **4c** with alkali metal thiocyanates. Whereas **2a** did not show any interaction with LiSCN,[5, 20] **4c** solubilized solid LiSCN in $CDCl_3$ and the peak of the benzene proton *ortho* to the nitrogen was shifted downfield by 0.14 ppm upon complexation at the nitrogens, leaving the other peaks almost unaffected. When NaSCN or KSCN was used instead, no solubilization occurred.

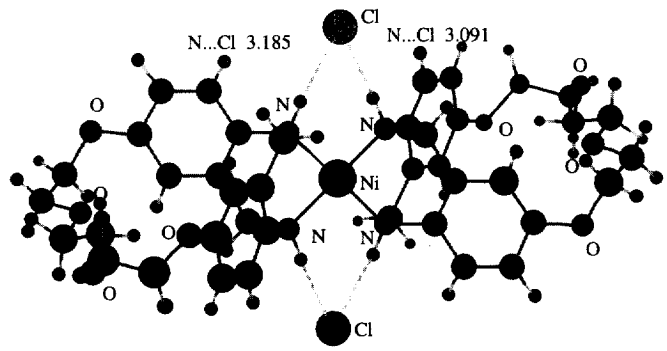

Figure 2. X-Ray structure of $\mathbf{4a}_2$•$NiCl_2$ complex. Hydrogen bondings between NH and Cl as indicated by short N...Cl distances (3.091 and 3.185Å) are shown.

Thus, **4a-c** would be useful in the existing asymmetric reactions in place of the chiral diamines currently used. The advantage of the trögerophane-derived diamines may then be the possibility that the ligand properties can be fine-tuned by (1) altering the chain length to get a suitable bite angle and (2) introducing a variety of functional groups at the nitrogens.

Structural studies of these ligands and their practical applications to asymmetric syntheses are now underway.

Acknowledgments

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17. **2a** (cubic crystals, mp 229.5-230 °C): the first component: colorless needles, mp 131-131.5 °C, $[\alpha]_D^{24}$ -63.2° (c 1.0, EtOH); the second component: colorless needles, mp 131.5-132 °C, $[\alpha]_D^{24}$ +64.8° (c 1.0, EtOH). **4a** (colorless fine needles, mp 171-172.5 °C): the first component: colorless needles, mp 185.5-186 °C, $[\alpha]_D^{24}$ +199.0° (c 0.7, EtOH), the second component: colorless needles, mp 186-186.5 °C, $[\alpha]_D^{24}$ -198.1° (c 0.7, EtOH).
18. $(\mathbf{4a})_2 \cdot NiCl_2 \cdot (CH_3NO_2)_2$: orange-yellow prisms from nitromethane. The details of the X-ray structural analysis will be reported elsewhere.
19. In addition to the well-known (-)-sparteine-mediated asymmetric syntheses using organolithium reagents,[a] a number of asymmetric organometallic reactions involving Li[b], Mg[c], Zn[d], Sn[e], and Pd[f] have been mediated by closely related ethylenediamine-based chiral ligands. (a) Nozaki, H; Aratani, T.; Toraya, T, and Noyori, R. *Tetrahedron* **1971**, *27*, 905-913, Okamoto, Y.; Suzuki, K.; Yuki, H. *J. Polymer Sci.* **1980**, *18*, 3041-3051. (b) Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585-4586, Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koza, K. *Tetrahedron* **1997**, *53*, 7191-7200. (c) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 1291-1292, (d) Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc. Chem. Commun.* **1989**, 741-742. (e) Kobayashi, S.; Uchino, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247-4252. (f) Kubota, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 8135-8138.
20. Although our original purpose of the polyether chain was to increase solubility of the trögerophanes because of its flexibility, the longer chain in **2b** is folded to allow complexation with LiSCN at the polyether moiety.[5]