Synthesis and Properties of a Novel Tetraazamacrocycle Containing Two Bispidine Units

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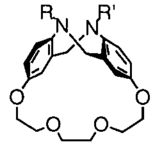
A novel cyclam-like macrocyclic tetramine **10** with two bispidine units was synthesized by coupling of bispidine **7** with bispidine bis(α-chloroacetamide) **8**, followed by reduction with DIBAL-H. The tetramine **10** revealed very strong basicity and lithium coordinating ability.

In our studies on Trögerophane-derived benzodiazocines **1**[1] we became interested in 3,7-diazabicyclo-[3.3.1]nonane (bispidine) **2** and its derivatives, because they also have two nitrogen lone pairs in close proximity. Bispidines have attracted many chemists over the years[2] with renewed interest in relation to the well-known asymmetric auxiliary (−)sparteine.[3] Although the two 6-membered rings in **2** favor boat-chair conformation in many cases,[4] once a proton or a metal cation is captured by the two nitrogen atoms, the conformation becomes fixed to chair-chair to form a rigid adamantane-like structure by H-bonding[5] or chelate bond formation.[6]



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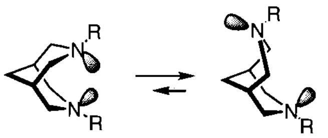

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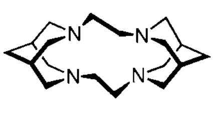
We thought, therefore, if two bispidine units were connected by two ethylene bridges as in **3**, the bispidine skeletons would be fixed in chair-chair conformation and preorganized for capturing a proton or metal ion. The structure of **3** resembles the well-known potent ligand cyclam **4** in its arrangement of nitrogens and ring size,[7] but we expected that **3** would be stronger in its ability because its nitrogens are tertiary and, once formed, protected by the cage structure. Actually, Hancock et al. made their efforts to prepare **3**[8] and Black et al. claimed isolation of a copper complex **5** from Mannich reaction of dibenzyl ketone and ethylenediamine in the presence of $Cu(OAc)_2$ in 1% yield.[9]

Here we report the synthesis of **10** as the first unequivocal example of this ring system. We selected 1,5-diphenylbispidine **7** as the bispidine unit, because it is readily available[10] and the four benzene rings in **10** would make the metal complexes more lipophilic and, thus, increase the usefulness in applications.



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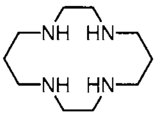

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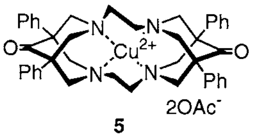

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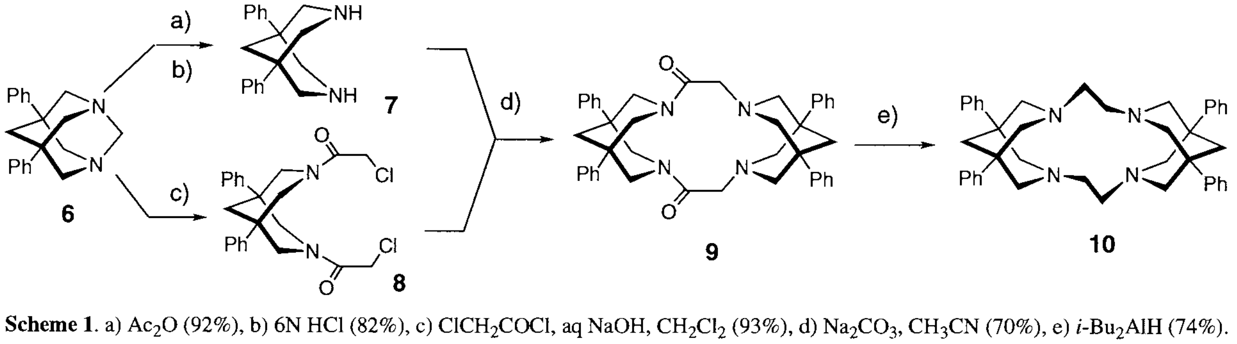
As shown in Scheme 1, the synthetic route is based on the method developed by Bradshaw et al.[11] and takes advantage of favorable parallel conformation and high reactivity of bis(α-chloroacetamide) **8**.[12] Thus, although poorly soluble **8** required the use of a Soxhlet apparatus for addition in the coupling reaction with **6**, the yield was as high as 70%.[12]

Reduction of amide **9** to amine **10** was not successful with the usual reagents, BH_3-THF and $LiAlH_4$.[13] They gave either an exceptionally stable borane complex or an N-C cleaved product **7** (34% yield), respectively. We found that *i*-Bu_2AlH (DIBAL-H) with KF workup[14] readily afforded the desired tetramine **10** in 74% yield.[13]

The free base **10** has unexpectedly low solubility in common organic solvents. However, addition of trifluoroacetic acid readily solubilized **10** in MeOH to form a diprotonated salt $2H^+$@**10**·$2CF_3COO^-$ in 93% yield, even with excess trifluoroacetic acid.[12] Although the very low solubility of **10** in water, acetonitrile, or dimethyl sulfoxide did not permit determination of $pK_{a1\text{-}a4}$ by titration, we could confirm that **10** was a much stronger base than the well-known Proton Sponge [PS, 1,8-bis(dimethylamino)naphthalene, pK_a 12.1 (in H_2O), 18.18 (in CH_3CN)].[16] Namely, when $2H^+$@**10**·$2CF_3COO^-$ was titrated with monitoring UV absorption of PS (λ_{max} 338 nm) and PSH (λ_{max} 286 nm), the amount of the diacid salt decreased in proportion to the added PS, behaving as a mono proton donor without any sign of releasing the last proton.

Lithium picrate (LiPic) and thiocyanate were also found to solubilize **10** in solvents as MeOH and THF. Even with excess Li salts, only mono Li complex **10**·LiPic[12] was obtained quantitatively. The Li complex readily picked up water and the Bohlmann bands found for **10** at 2756 and 2731 cm^{-1} in the IR



Scheme 1. a) Ac_2O (92%), b) 6N HCl (82%), c) $ClCH_2COCl$, aq NaOH, CH_2Cl_2 (93%), d) Na_2CO_3, CH_3CN (70%), e) *i*-Bu_2AlH (74%).

spectrum disappeared and a singlet appeared at δ 10.57 ppm in the ^{1}H NMR spectrum for a proton captured from water. Since **10** itself did not show such interaction with water, the Li^+ apparently brought about the interesting entrainment effect.

This Li complexation proved to be exceptionally strong. When **10** was added to a 4.37×10^{-5} M solution of LiPic in THF in molar ratios shown in Figure 1, the band at 346.5 nm underwent bathochromic shift to 370 nm (isosbestic point at 353 nm) as a result of transformation from a tight ion pair Li^+Pic^- to a ligand-separated ion pair Li^+|**10**|Pic^-.[17] Above the ratio of 2.28 no more change was observed and LiPic was assumed to be fully converted to Li^+|**10**|Pic. The formation constant K was thus calculated as 2.2×10^6 (log K = 6.34), which is much higher than the reported value (log K = 3.8) for complexation of lithium 2,4-dinitrophenolate with hexamethyl cyclam in THF-$CHCl_3$ (4:1).[18]

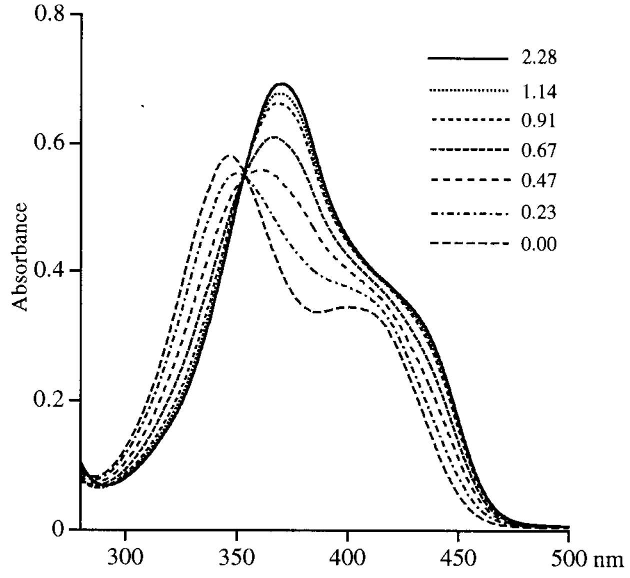


Figure 1. Spectral changes of LiPic (4.37×10^{-5} mol/L) in THF on addition of **10** in molar ratios shown.

This fact prompted us to examine **10** as the ligand for extraction of Li ion. Although, on shaking an aqueous LiPic solution with a $CHCl_3$ solution of **10**, Pic ion was completely transferred to the $CHCl_3$ phase, the same happened with NaPic. Since Na^+ appears to be too large to fit to **10** and actually no Na^+ was detected in the extracted organic phase by flame reaction, it may be concluded that the Pic ion was transferred not as the Li complex, but simply as the picric acid salt of highly basic **10**.

In preliminary studies Cu(II) and Ni(II) salts were added to a solution of **10** resulting in immediate color changes: for $Cu(ClO_4)_2$ in CH_3CN from light blue (λ_{max} 759 nm) to violet blue (λ_{max} 548 nm) and for $Ni(ClO_4)_2$ from light green to greenish yellow. However, no crystalline complexes could be isolated and **10** was recovered unchanged upon concentration. These results are in contrast to the isolation of Cu complexes of bispidine and its derivatives and, in particular, **5**, In order to elucidate the unique characteristics of this new pentacyclic tetramine, we are currently synthesizing the parent **3** which will not have solubility problems.

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8: colorless plates ($ClCH_2CH_2Cl$), mp 229.5–230 °C; IR (Nujol): $\nu_{C=O}$ 1643, 1630 cm^{-1}.
9: colorless plates (CH_2Cl_2-MeOH), mp 289.5–291.5 °C (dec); IR (Nujol): ν_{CH} 2757, 2731, $\nu_{C=O}$1649, 1638 cm^{-1}; FAB-MS *m/z* 637.5 [$(M+H)^+$].
10: colorless needles (C_6H_6), mp 310–310.5 °C (dec); IR (Nujol) ν_{CH} 2756, 2730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (8H, d, *J* = 7.5 Hz), 7.40 (8H, dd, *J* = 7.5, 7.0 Hz), 7.27 (4H, t, *J* = 7.0 Hz), 3.39 (8H, d, *J* = 10.6 Hz), 2.46 (8H, s), 2.21 (8H, d, *J* = 10.0 Hz), 2.15 (4H, s); FAB-MS *m/z* 609.4 $(M+H)^+$.
$2H^+$@**10**·$2CF_3COO^-$: colorless plates (MeOH), mp 306.5–307 °C (dec); IR (Nujol) ν_{COO-} 1749, ν_{CF} 1260, 1142 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 10.77 (2H, s), 7.56 (8H, d, *J* = 7.5 Hz), 7.49 (8H, dd, *J* = 7.5, 7.0 Hz), 7.40 (4H, t, *J* = 7.0 Hz), 4.05 (8H, d, *J* = 11.5 Hz), 3.22 (8H, s), 3.04 (8H, dd, *J* =11.5, 4.0 Hz; the coupling of 4.0 Hz with the included proton vanished upon irradiation at 10.77 ppm), 2.52 (4H, s); FAB-MS *m/z* 723.4 $(M-CF_3COO)^+$, 609.4 $(M-2CF_3COO+H)^+$.
Li^+@**10**·Pic^-: yellow needles (CH_3CN-Et_2O), mp 242.5–244 °C (dec.); IR (Nujol): ν_{NO_2} 1365, 1332 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.57 (1H, s), 8.75 (2H, s), 7.42 (8H, d, *J* = 7.0 Hz), 7.35 (8H, dd, *J* = 7.0, 7.5 Hz), 7.29 (4H, t, *J* = 7.5 Hz), 3.69 (8H, d, *J* = 10.5 Hz), 2.93 (8H, s), 2.59 (8H, d, *J* = 11.0 Hz), 2.34 (4H, s).
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