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Synthesis and Characterisation of Macrocyclic Diamino Chiral Crown Ethers

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Abstract: A benign and efficient synthesis of chiral macrocyclic ‘aza-crown’ ethers of varying ring size is reported. The synthesis involves a Schiff base condensation of ether linked dialdehydes of varying chain length and (1*R*,2*R*)-(–)-1,2-diaminocyclohexane under mild conditions to yield the macrocycles, which are subsequently reduced to yield the diamino analogues.

Keywords: Chiral diamino macrocycles, ether linked dialdehydes

Introduction

In 1998 Kaupp reported the facile solvent-free condensation of aryl amines and benzaldehyde derivatives to produce azo-methines [1]. This is an advantageous and facile route as it negates the generation of excessive waste whilst proceeding more efficiently than corresponding solution phase methodologies. This approach has subsequently been extended to corresponding amine derivatives such as the tetrahydroquinazolines [2]. More recently, we have adopted an analogous, simple procedure that allows for the efficient generation of some macrocycles derived from the reduction of

In most cases the reduced macrocyclic products **3** were isolated as oils. Subsequent purification involved the precipitation of hydrochloride salts by reaction with excess hydrochloride in ether. The ^1H - and ^{13}C -NMR spectra of the respective Schiff bases **2** and diamino products **3** were consistent with the assigned structures in all cases. There was no spectroscopic evidence for the presence of any imine protons once the reduction had been performed. This reduction step needed to be conducted under relatively forcing conditions, utilising a vast excess of reducing agent and at elevated temperature, as the macrocycles **2** were poorly soluble in ethanol.

All of the macrocycles synthesised are optically active. The absence of peaks at higher m/z values than that expected for the corresponding parent ion (LH^+) in the electrospray ionisation mass spectra attest to exclusive formation of 1:1 condensation products. The Schiff base infrared spectra confirms the presence of the imine $\text{C}=\text{N}$ stretch with a sharp band in the region $1630\text{--}1640\text{ cm}^{-1}$. These bands are absent in the reduced product. The HCl salts are all hygroscopic, and in the case of **3a** and **3d**, there was microanalytical as well as spectral evidence for the formation of 1:1 hydrates. In addition, the salts appear to complex common solvents, which are subsequently difficult to remove, even under vacuum at elevated temperature. The presence of solvates, was inferred from the existence of corresponding signals in ^1H -NMR and infrared spectra. Repeated attempts to crystallise the macrocycles resulted in oils or glasses, though the HCl salts are afforded as finely divided white solids.

Conclusions

We have developed a facile and high yielding route for the formation of a novel class of chiral diamino macrocyclic compounds incorporating ether chains.

Acknowledgements

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Experimental

General

All reagents were of 98 % purity or greater and used as obtained from the supplier unless noted otherwise. Grinding experiments were performed with porcelain mortar and pestles, which were rinsed with acetone and dried prior to use. All melting points were determined on an Electrochemical digital melting point apparatus. ^1H -NMR and ^{13}C -NMR spectra were recorded on either a Varian Mercury 300 MHz or Bruker DRX400MHz. spectrometers. Chemical shifts were referenced relative to CDCl_3 or CD_3OD . Electrospray Mass Spectroscopy (ESI) was carried out on a Micromass Platform II API QMS Electrospray Mass Spectrometer with cone voltage at 35 V, using acetone as the mobile phase. Analyses were conducted both in positive (ESI^+) and negative (ESI^-) mode. Infrared spectroscopy was

carried out on a Perkin Elmer FTIR-1600 with samples were prepared as KBr discs. Specific rotations were measured on a Hewlett Packard Polar 3005 polarimeter. Microanalyses were conducted on the HCl salts of the reduced macrocycles.

General Procedure for the Synthesis of Diamino Macrocycles

An equimolar quantity of the relevant dialdehyde **1** together with (1*R*,2*R*)-(-)-1,2-diaminocyclohexane was ground using a mortar and pestle at room temperature for approximately 5 minutes. The resultant powder was washed with cold ethanol; in the case of **2c** and **2d** the corresponding dialdehyde precursors are oils at room temperature and, consequently, the condensation was carried out in absolute ethanol at room temperature. After 20-30 min the oily products began to separate from solution; after 4.5 h the supernatant was decanted yielding the desired Schiff base. The larger macrocyclic products are all pale yellow oils, (only **2a** is a solid), and were purified by washing with hot ethanol. The respective Schiff bases were combined with 10 mol equiv. of NaBH₄ in absolute ethanol. The reaction mixture was heated under reflux for 4-5 h, cooled and quenched with distilled water. Solvent was removed *in vacuo* and the product extracted into dichloromethane. The organic layer was washed twice with brine, dried with MgSO₄ and concentrated to afford the products as pale yellow oils. Spectroscopic data is given for the free base. The dihydrochloride salts were obtained by dissolving the oils in dichloromethane and adding an excess HCl in ether. White or pale yellow gummy solids formed instantly which were triturated and washed with hexane and filtered off.

1,12-Diaza-3,4;9,10-dibenzo-13,14-cyclohexo-5,8-dioxacyclobutadecane (2a). Isolated as a yellow solid (89%); m.p. 124-126 °C; ¹H-NMR (CDCl₃) δ: 1.41 (bs, 2H, 2 x CH), 1.74-1.98 (bm, 6H, 2 x CH & 2 x CH₂), 3.36 (bs, 2H, 2 x -C-CH-N=), 3.85-3.90 (m, 2H, 2 x Ar-OCH), 4.05-4.11 (m, 2H, 2 x Ar-O-CH-), 6.77-6.89 (2d, 4H, Ar-CH), 7.26 (m, 2H, Ar-CH), 7.83 (d, 2H, Ar-CH), 8.52 (s, 2H, -N=CH); ¹³C-NMR (CDCl₃) δ: 24.5, 32.9, 66.7 (-C-NH=), 73.7 (-C-O-C), 112.1 (Ar-C), 120.1 (Ar-C), 125.4 (Ar-C), 127.5 (Ar-C), 131.3 (Ar-C), 157.0 (Ar-C), 157.7 (-NH=C-); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2926 and 2855 (C-H methylene stretch), 1634 (C=N stretch), 1599, 1486 and 1450 (C=C aromatic ring stretch), 1238 (aryl-O-CH₂ stretch), 1051 (in plane C-H bend), 735 (out of plane C-H bend), 428 (out of plane ring C=C bend); ESI-MS for C₂₂H₂₄N₂O₂ (MH⁺): Calc 349.2; Found 349.2; [α]_D²⁶ = -30.0 (c = 0.012, CH₂Cl₂).

1,15-Diaza-3,4;12,13-dibenzo-16,17-cyclohexo-5,8,11-trioxacyclohexaundecane (2b). Isolated as a pale yellow gum (95%); ¹H-NMR (CDCl₃) δ: 1.44 (bs, 2H, 2 x CH), 1.80 (bs, 6H, 2 x CH & 2 x CH₂), 3.39 (bs, 2H, 2 x -C-CH-N=), 3.74 (t, 4H, -CH₂-O-CH₂), 3.90-4.00 (m, 2H, 2 x Ar-O-CH-), 4.02-4.15 (m, 2H, 2 x Ar-O-CH-), 6.80 (d, 2H, Ar-CH), 6.86 (t, 2H, Ar-CH) 7.24 (2t, 2H, Ar-CH), 7.82 (2d, 2H, Ar-CH), 8.61 (s, 2H, -N=CH-); ¹³C-NMR (CDCl₃) δ: 21.2, 34.1, 68.4 (-C-NH=), 69.6 (-C-O-C), 71.2 (Ar-C-O-), 112.4 (Ar-C), 120.7 (Ar-C), 125.8 (Ar-C), 128.0 (Ar-C) 131.1 (Ar-C), 157.1 (Ar-C-), 157.9 (-NH=C-); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2928 and 2855 (C-H methylene stretch), 1634

(C=N stretch), 1601, 1491 and 1450 (C=C aromatic ring stretch), 1243 (aryl-O-CH₂ stretch), 1055 (in plane C-H bend), 751 (out of plane C-H bend); ESI-MS for C₂₄H₂₈N₂O₃ (MH⁺): Calc. 393.2; Found 393.1; $[\alpha]_D^{26} = -28.1$ (c = 0.005, CH₂Cl₂).

1,18-Diaza-3,4;15,16-dibenzo-19,20-cyclohexo-5,8,11,14-tetraoxacycloctadodecane (2c). Isolated as a viscous yellow oil (95%); ¹H-NMR (CDCl₃) δ: 1.46 (bs, 2H, 2 x CH), 1.82 (bs, 6H, 2 x CH & 2 x CH₂), 3.4 (bs, 2H, 2 x -C-CH-N=), 3.70 (s, 4H, -O-CH₂-CH₂-O-), 3.75 (t, 4H, 2 x Ar-O-CH₂-CH₂-O-), 3.88-4.00 (m, 2H, 2 x Ar-O-CH), 4.02-4.13 (m, 2H, 2 x Ar-O-CH), 6.77 (d, 2H, Ar-CH), 6.86 (t, 2H, Ar-CH) 7.22 (2t, 2H, Ar-CH), 7.81 (2d, 2H, Ar-CH), 8.61 (s, 2H, -N=CH-); ¹³C-NMR (CDCl₃) δ: 24.5, 32.9, 67.8 (-C-NH=), 69.5 (Ar-O-C-C-O-), 70.8 (O-C-C-O-), 73.9 (Ar-O-C-), 112.1 (Ar-C), 120.9 (Ar-C), 125.2 (Ar-C), 127.8 (Ar-C) 131.0 (Ar-C), 156.9 (Ar-C-), 158.0 (-NH=C-); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2926 and 2855 (C-H methylene stretch), 1635 (C=N stretch), 1600, 1488 and 1450 (C=C aromatic ring stretch), 1247 (aryl-O-CH₂ stretch), 1056 (in plane C-H bend), 754 (out of plane C-H bend), 428 (out of plane ring C=C bend); ESI-MS for C₂₆H₃₂N₂O₄ (MH⁺): Calc. 437.2; Found 437.3; $[\alpha]_D^{25.1} = -35.2$ (c = 0.010, CH₂Cl₂).

1,21-Diaza-3,4;18,19-dibenzo-22,23-cyclohexo-5,8,11,14,17-pentaoxacyclodecatridecane (2d). A viscous yellow oil (95%); ¹H-NMR (CDCl₃) δ: 1.48 (bt, 2H, 2 x CH), 1.83 (bs, 6H, 2 x CH & 2 x CH₂), 3.41 (bs, 2H, 2 x -C-CH-N=), 3.68 (s, 8H, -O-CH₂-CH₂-O-CH₂-CH₂-O-) 3.74 (t, 4H, 2 x Ar-O-CH₂-CH₂-), 3.90-4.00 (m, 2H, 2 x Ar-O-CH), 4.02-4.12 (m, 2H, 2 x Ar-O-CH), 6.77 (d, 2H, Ar-CH), 6.86 (t, 2H, Ar-CH) 7.23 (2t, 2H, Ar-CH), 7.80 (2d, 2H, Ar-CH), 8.60 (s, 2H, -N=CH-); ¹³C-NMR (CDCl₃) δ: 24.4, 32.9, 67.8 (-C-NH=), 69.4 (Ar-O-C-C-O-), 70.6 (Ar-O-C-C-O-C-), 70.7 (Ar-O-C-C-O-C-C-O-) 73.8 (Ar-O-C), 112.1 (Ar-C), 120.7 (Ar-C), 125.2 (Ar-C), 127.3 (Ar-C) 131.2 (Ar-C), 157.0 (Ar-C-), 157.8 (-NH=C-); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2929 and 2855 (C-H methylene stretch), 1636 (C=N stretch), 1600, 1488 and 1449 (C=C aromatic ring stretch), 1254 (aryl-O-CH₂ stretch), 1045 (in plane C-H bend), 754 (out of plane C-H bend), 438 (out of plane ring C=C bend); ESI-MS for C₂₈H₃₆N₂O₅ (MH⁺): Calcd 481.3; Found 481.5; $[\alpha]_D^{23.7} = -52.5$ (c = 0.012, CH₂Cl₂).

1,12-Diamino-3,4;9,10-dibenzo-13,14-cyclohexo-5,8-dioxacyclobutadecane (3a). Isolated as an orange oil (80%); ¹H-NMR (CDCl₃) δ: 0.93 (bt, 2H, 2 x CH), 1.14 (bt, 2H, 2 x CH), 1.64 (bd, 2H, 2 x CH), 2.00 (bd, 2H, 2 x CH), 2.13 (bd, 2H, 2 x -CH-N-), 3.58 (d, 2H, J = 13.2 Hz, 2 x -NH-CH-CH₂-Ar-), 3.81 (d, 2H, J = 13.5 Hz, -NH-CH-CH₂-Ar-), 5.58 (s, 4H, -O-CH₂-CH₂-O-), 6.92 (bt, 2H, Ar-CH), 7.02-7.20 (m, 4H, Ar-CH), 7.25 (bd, 2H, Ar-CH); ¹³C-NMR (CDCl₃) δ: 24.9, 31.3, 45.6 (-NH-C-), 60.8 (-C-NH-), 90.6 (-O-C-O-), 111.8 (Ar-C), 122.1 (Ar-C), 127.8 (Ar-C), 129.5 (Ar-C) 130.1 (Ar-C), 154.7 (Ar-C); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2926 and 2855 (C-H methylene stretch), 1634 (C=N stretch), 1599, 1486 and 1450 (C=N aromatic ring stretch), 1238 (aryl-O-CH₂ stretch), 1051 (in plane C-H bend), 735 (out of plane C-H bend), 428 (out of plane ring C=C bend); ESI-MS for

$C_{22}H_{28}N_2O_2$ (MH^+): Calcd 353.2; Found 353.4; Anal. Calc. for $C_{22}H_{28}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 59.6; H, 7.3; N, 6.3. Found: C, 59.4; H, 7.1; N, 6.1; $[\alpha]_D^{24.5} = -48.1$ ($c = 0.018$, CH_3OH).

1,15-Diamino-3,4;12,13-dibenzo-16,17-cyclohexo-5,8,11-trioxacyclohexaundecane (3b). Isolated as a pale orange oil (91%); 1H -NMR ($CDCl_3$) δ : 1.09 (bs, 4H, $-CH_2-CH_2-$), 1.62 (bs, 2H, 2 x CH), 2.07 (d, 2H, 2 x CH), 2.19 (bs, 2H, 2 x $-CH-NH-$), 2.78 (bs, 2H, NH), 3.60 (d, 2H, $J = 13.5$ Hz, 2 x $-NH-CH-$), 3.67 (t, 4H, $-CH_2-O-CH_2-$), 3.92 (d, 2H, $J = 13.2$ Hz, 2 x $-NH-CH-$), 3.96 (t, 4H, 2 x Ar-O- CH_2), 6.76 (d, 2H, Ar-CH), 6.87 (t, 2H, Ar-CH), 7.15-7.28 (m, 4H, Ar-CH); ^{13}C -NMR ($CDCl_3$) δ : 2425.0, 31.2, 45.9 ($-NH-C-$), 60.7 ($-C-NH-$), 67.5 ($-C-O-C-$), 69.8 (Ar-O- $C-$), 111.3 (Ar-C), 120.7 (Ar-C), 127.9 (Ar-C), 129.2 (Ar-C), 129.6 (Ar-C), 156.7 (Ar-C); IR (cm^{-1}): 3080 (aromatic C-H stretch), 2920 and 2855 (C-H methylene stretch), 1601, 1490 and 1450 ($C=C$ aromatic ring stretch), 1240 (aryl-O- CH_2 stretch), 1052 (in plane C-H bend), 750 (out of plane C-H bend); ESI-MS for $C_{24}H_{32}N_2O_3$ (MH^+): Calcd 397.2; Found 397.3; Anal. Calc. for $C_{24}H_{32}N_2O_3 \cdot 2HCl \cdot 2H_2O$: C, 57.0; H, 7.6, N, 5.5. Found C, 56.8; H, 7.6; N, 5.2; $[\alpha]_D^{24.5} = -51.2$ ($c = 0.012$, CH_3OH).

1,18-Diamino-3,4;15,16-dibenzo-19,20-cyclohexo-5,8,11,14-tetraoxacyclooctadodecane (3c). Isolated as a pale yellow oil (92%); 1H -NMR ($CDCl_3$) δ : 1.03 (bs, 2H, 2 x CH), 1.21 (bt, 2H, 2 x CH), 1.68 (bd, 2H, 2 x CH), 2.11-2.21 (m, 4H, 2 x CH & 2 x $-CH-NH-$), 3.65 (d, 2H, $J = 13.5$ Hz, 2 x $-NH-CH-$), 3.61 (s, 4H, $-O-CH_2-CH_2-O-$), 3.70 (t, 4H, 2 x Ar-O- CH_2-CH_2-O-), 3.89 (d, 2H, $J = 13.5$ Hz, 2 x $-NH-CH-$), 4.02 (t, 4H, 2 x Ar-O- CH_2-), 6.77 (d, 2H, Ar-CH), 6.87 (t, 2H, Ar-CH), 7.13-7.25 (m, 4H, Ar-CH); ^{13}C -NMR ($CDCl_3$) δ : 25.0, 31.3, 45.9 ($-NH-C-$), 60.7 ($-C-NH-$), 67.4 (Ar-O- $C-C-$), 69.7 ($-O-C-C-O-$), 70.8 (Ar-O- $C-$), 111.2 (Ar-C), 120.5 (Ar-C), 127.7 (Ar-C), 129.4 (Ar-C), 129.5 (Ar-C), 156.7 (Ar-C); IR (cm^{-1}): 3080 (aromatic C-H stretch), 2936 and 2860 (C-H methylene stretch), 1603, 1497 and 1458 ($C=C$ aromatic ring stretch), 1248 (aryl-O- CH_2 stretch), 1052 (in plane C-H bend), 754 (out of plane C-H bend); ESI-MS for $C_{26}H_{36}N_2O_4$ (MH^+): Calc 441.3; Found 441.5; Anal. Calc. for $C_{26}H_{36}N_2O_4 \cdot 2HCl$: C, 60.8; H, 7.5; N, 5.5. Found: C, 60.8; H, 7.5; N, 5.3; $[\alpha]_D^{25.9} = -26.9$ ($c = 0.024$, CH_3OH).

1,21-Diamino-3,4;12,13-dibenzo-18,19-cyclohexo-5,8,11,14,17-pentaoxacyclodecatridecane (3d). A pale yellow oil (91%); 1H -NMR ($CDCl_3$) δ : 1.00-1.26 (m, 4H, $-CH_2-CH_2-$), 1.68 (bd, 2H, 2 x CH), 2.10 (d, 2H, 2 x CH), 2.23 (bs, 2H, 2 x $-CH-NH-$), 2.33 (bs, 2H, NH), 3.60 (bs, 8H, $-O-CH_2-CH_2-O-CH_2-CH_2-O-$), 3.61 (d, 2H, $J = 13.5$ Hz, 2 x $NH-CH-$), 3.69 (t, 4H, 2 x Ar-O- CH_2-CH_2-O), 3.92 (d, 2H, $J = 13.5$ Hz, 2 x $-NH-CH-$), 4.01 (t, 4H, 2 x Ar-O- CH_2-), 6.77 (d, 2H, Ar-CH), 6.88 (t, 2H, Ar-CH), 7.17-7.25 (m, 4H, Ar-CH); ^{13}C -NMR ($CDCl_3$) δ : 24.9, 31.1, 45.9 ($-NH-C-$), 60.5 ($-C-NH-$), 67.3 (Ar-O- $C-C-O-$), 69.5 ($-O-C-C-O-C-C-O-$), 70.5 (Ar-O- $C-$), 70.6 (Ar-O- $C-$), 111.1 (Ar-C), 120.4 (Ar-C), 127.7 (Ar-C), 129.0 (Ar-C), 129.5 (Ar-C), 156.6 (Ar-C); IR (cm^{-1}): 3080 (aromatic C-H stretch), 2924 and 2860 (C-H methylene stretch), 1602, 1492 and 1458 ($C=C$ aromatic ring stretch), 1259 (aryl-O- CH_2 stretch), 1052 (in plane C-H bend), 754 (out of plane C-H bend), 438 (out of plane ring $C=C$).

bend); ESI-MS for $C_{28}H_{40}N_2O_5$ (MH^+): Calc. 485.3; Found 485.5; Anal. Calc. for $C_{28}H_{40}N_2O_5 \cdot 2HCl \cdot H_2O$: C, 58.4; H, 7.7; N, 4.9. Found: C, 58.7; H, 8.0; N, 4.8; $[\alpha]_D^{23.8} = -25.7$ ($c = 0.019$, CH_3OH).

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Sample Availability: Available from the authors.

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