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The synthesis of novel chiral macrocyclic and polymeric amines containing a *trans*-1,2-diaminocyclohexane system

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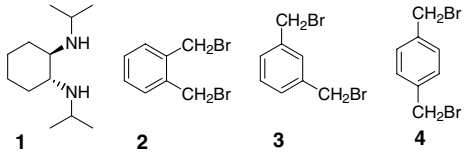
Abstract—The reactions of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane with isomeric benzylic dibromides gave heterocycles and macrocycles. Additionally a reaction with adipoyl chloride gave a polymeric amido carboxylic acid that could be readily reduced to the corresponding polyamino alcohol using the $NaBH_4/I_2$ reagent system.

1. Introduction

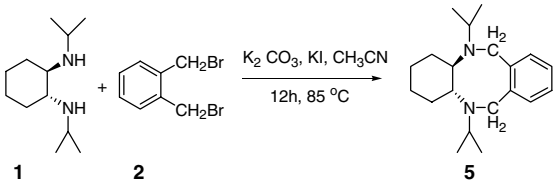
Chiral macrocycles have a wide range of applications in enantiomeric recognition,[1] for use in the preparation of chiral stationary phases[2] and in catalysis.[3] Some metal complexes of chiral macrocycles are also useful as chiral shift reagents[4] while other chiral macrocycles have been shown to exhibit anti-fungal activities.[5] As a result, the synthesis of chiral macromolecules has attracted considerable attention of chemists. In particular, C_2 symmetric macrocycles have been extensively studied because of their structural architecture, which is suitable for complex formation both with metals and host molecules.[6] It has been reported that macrocycles synthesized from chiral 1,2-diaminocyclohexane have been used as molecular receptors for peptides[7] and in the enantiomeric recognition of amino acids.[8] In addition, 1,2-diaminocyclohexane derivatives have been used as chiral ligands and catalysts in various asymmetric transformations.[9] Therefore, systematic investigation on the synthesis of macromolecules from this versatile amine should lead to fruitful results.[10] We herein report on the results of the synthesis of chiral macrocycles using (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **1**.

2. Results and discussion

(*R*,*R*)-*N*,*N*′-Diisopropyl-1,2-diaminocyclohexane **1** was synthesized in 65% yield in a single step by direct alkylation of (*R*,*R*)-1,2-diaminocyclohexane using a large excess of isopropyl bromide.[11]



We have then examined the reaction of the secondary amine **1** with the benzylic dibromide derivatives **2**, **3** and **4** to obtain chiral heterocycles and macrocycles. The [1 + 1] heterocyclic product **5** was obtained in 80% yield in the reaction of the diamine **1** with **2** (Eq. 1). The presence of macrocycles, if any, in the sample could not be detected by ^{1}H NMR, ^{13}C NMR and mass spectral analysis.



(1)

The reaction of diamine **1** with the 1,3-dibromide derivative **3** gave the corresponding macrocycle **6** (Eq. 2), in addition to high molecular weight macrocyclic and oligomeric products.[12]

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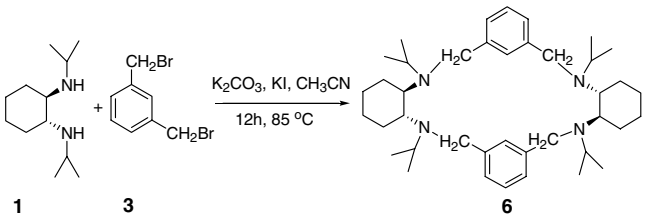


(2)

Separation of the products was achieved by treating the mixture with oxalic acid in DCM. The diacid complex of the high molecular weight oligomers precipitated from the solution. Macrocycle **6**, obtained from the filtrate, was purified by chromatography. The ^{1}H NMR spectrum (400 MHz) of compound **6** exhibited broad signals at 20 °C with two sets of signals for the benzylic as well as for the isopropyl groups. However, the signals resolved better at 0 °C (Fig. 1).

The X-ray crystal structure analysis of the crystals of compound **6** re-crystallized from hexane showed that there were two types of isopropyl groups (Fig. 2).[13] Furthermore, the aryl rings are equivalent but in each ring the benzylic CH_2, the quaternary carbon atoms and the 3,5-carbon atoms are not equivalent. Although, the conformations of the molecule in the crystal and in solution need not be the same, the six aromatic signals in the ^{13}C NMR spectrum indicates that the conformations of the compound in the crystal and in solution at 0 °C are similar.

A mixture of CH_2Cl_2/THF soluble and insoluble fractions was obtained in the condensation of diamine **1** with 1,4-dibromide **4**. The mass spectral analysis (FAB) of the soluble fraction indicated the presence of macrocycles **7** (>95%) and **8** (<5%). Macrocycle **7** (0.2 g) could be isolated in its pure form from the mixture (0.24 g) by precipitation using oxalic acid in dichloromethane. Attempts to obtain macrocycle **8** in its pure form from the mother liquor were unsuccessful. Macrocycle **7** was analysed by single crystal X-ray analysis of the crystals obtained by re-crystallization from toluene

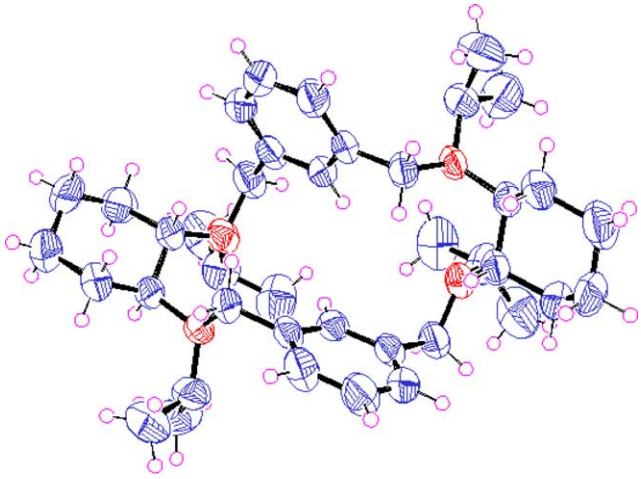
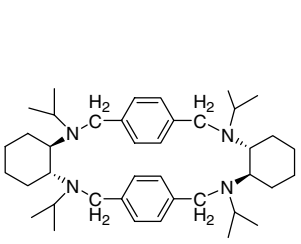


Figure 2. ORTEP diagram of the compound **6**.

(Fig. 3).[14] The crystal structure revealed that there were two types of isopropyl groups and that the diagonal isopropyl groups were equivalent.



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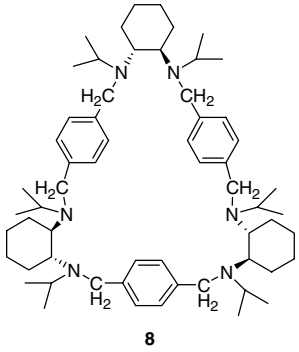

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Macrocycle **7** also displayed broad ^{1}H NMR (400 MHz) signals at 20 °C (Fig. 4). The ^{1}H NMR signals were resolved better at lower temperatures and indicate the presence of two types of isopropyl groups (Fig. 4). Furthermore, the benzene rings were equivalent, but in each ring, the quaternary carbon atoms and the 1,3-carbon

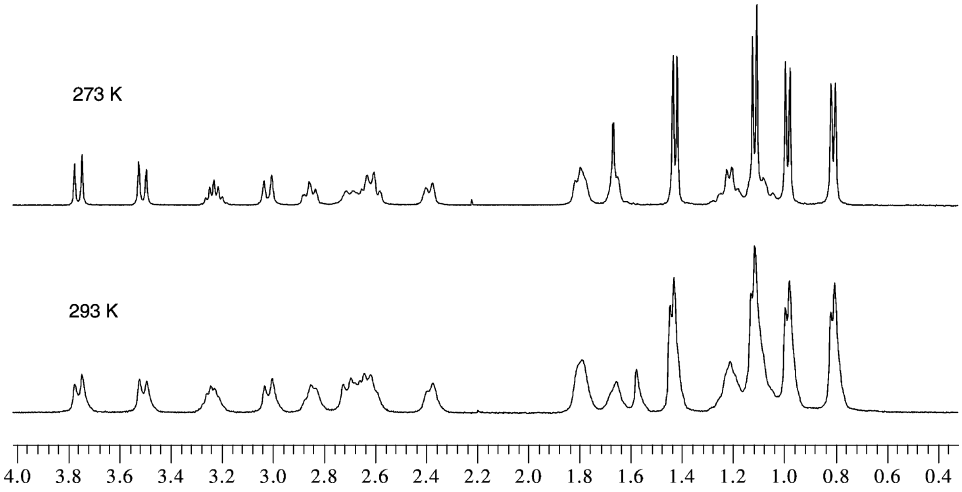


Figure 1. ^{1}H NMR spectra (400 MHz) of compound **6** (aliphatic region).

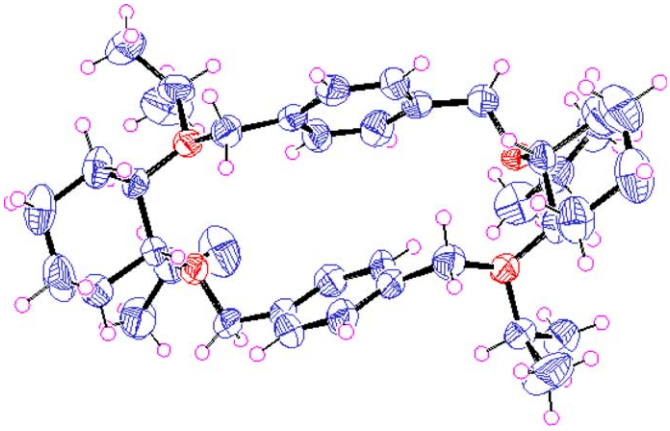


Figure 3. ORTEP diagram of the product **7**.

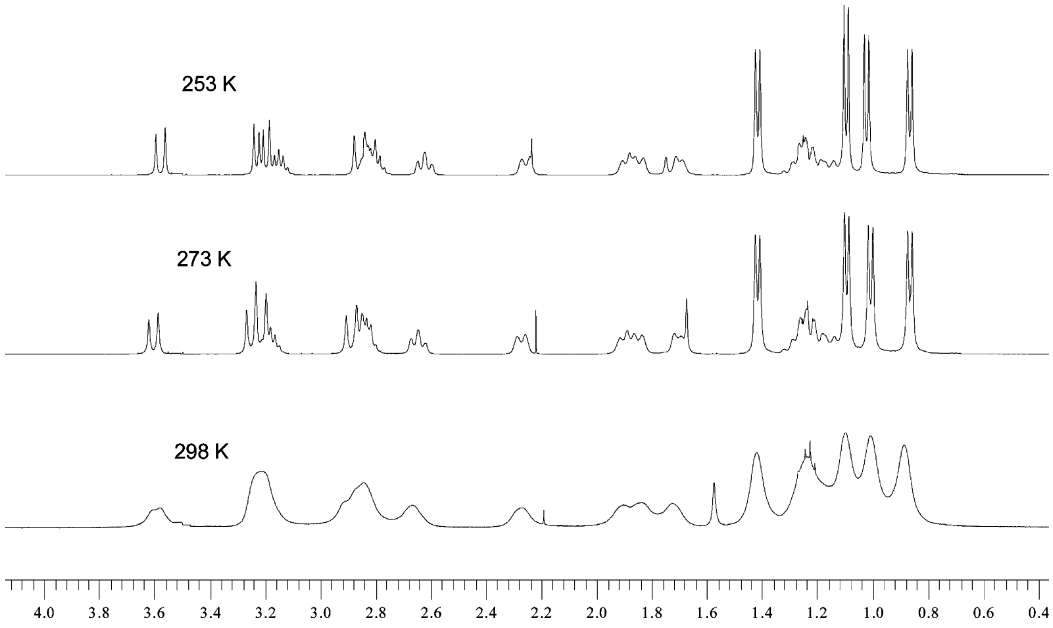


Figure 4. ^{1}H NMR spectra of compound **7** (aliphatic region).

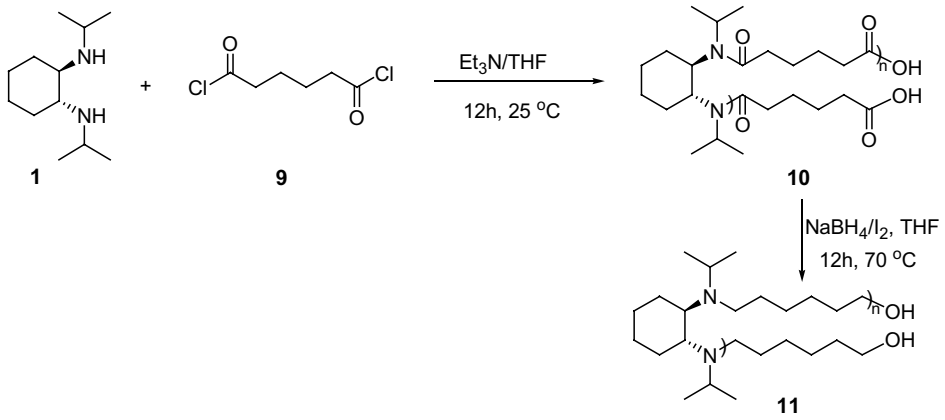
atoms were not equivalent. Although, the conformation in solution and crystal structure need not be the same, the four aromatic signals in the ^{13}C NMR spectrum instead of the two signals expected for a symmetrical 1,4-disubstitution, indicates that the conformations in the crystal and in solution at low temperatures are similar.

We next examined the possibility of the preparation of macrocycles containing aliphatic spacer groups. Diamine **1** failed to react with dibromide like 1,6-dibromohexane under various conditions. Therefore, we carried out the condensation of diamine **1** with adipoyl chloride **9** (Scheme 1).

In contrast to the macrocyclic products formed using aromatic benzylic bromides, in this case macrocyclic products were not obtained. The IR spectrum of the product exhibited signals at 1741 and 1631 cm^{-1} in addition to the signal at 3476 cm^{-1}. The signals observed at 172 and 171 ppm in the ^{13}C NMR spectrum of product **10** clearly confirm that this product is an amide with carboxylic acid end groups. Gel permeation chromatography showed that the average molecular weight of this polyamide-carboxylic acid **10** was 27499. Polymer **10** was readily reduced by $NaBH_4/I_2$ to obtain the corresponding polyamino alcohol.[15] The alcoholic end group can be easily protected as OCH_3 group by reaction with NaH/CH_3I.

3. Conclusion

In conclusion, we have developed methods of synthesis and isolation of a series of new chiral macrocyclic amines. Additionally, polymeric amide-carboxylic acid and amino alcohol have been readily accessed following simple protocols. Since chiral macrocycles have proven



Scheme 1.

applications, the readily accessible macrocycles have good synthetic potential.

4. Experimental section

Infrared spectra were recorded on Perkin–Elmer IR spectrophotometer Model 1310. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AV-400 spectrometers with chloroform-*d* as a solvent and TMS as the reference ($\delta = 0$ ppm). Coupling constants *J* are in Hz. The mass spectra were recorded on an Autospec Mass Spectrometer. Elemental analyses were carried out on a Flash EA 1112 series analyzer. Optical rotations were measured in an AUTOPOL-II automatic polarimeter (readability ±0.01). Chromatography was carried out using Acme's silica gel (100–200 mesh) and neutral alumina. Solvents were dried using the standard procedures. *cis*/*trans* mixture of 1,2-diaminocyclohexane was resolved following a reported procedure.[16] The dibromides were synthesized from the corresponding diacids by reduction[15] followed by reaction with HBr.

4.1. General procedure for the macrocyclisation of the diamine 1

To a solution of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **1** (0.5 g, 2.5 mmol) in acetonitrile (40 mL) was added the dibromide (0.658 g, 2.5 mmol), K_2CO_3 (2 g), KI (20 mg) and the mixture then stirred under reflux for 12 h. The solids were filtered off and extracted with DCM (2×30 mL) and water (30 mL). The organic extracts were dried over Na_2SO_4 and the residue evaporated. The products were purified either by column chromatography or by treatment with oxalic acid in DCM.

4.2. (4a*R*,11a*R*)-5,10-Diisopropyl-1,2,3,4,6,11-hexahydrodibenzo[*b*,*f*][1,4]diazocine 5

Yield: 80% (0.6 g); $[\alpha]_D^{25} = +63.0$ (*c* 0.4, 1 M HCl); IR (neat, cm^{-1}): 3058, 2927, 1448, 1170; ^{1}H NMR (200 MHz; $CDCl_3$) δ_H 7.09 (br s, 4H), 4.49 (d, *J* = 13.4 Hz, 2H), 3.82 (d, *J* = 13.5 Hz, 2H), 3.17 (septet, *J* = 6.4 Hz, 2H), 2.65 (m, 2H), 1.66 (m, 5H), 1.32 (m, 3H), 1.11 (d, *J* = 6.4 Hz, 12H); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 140.7, 129.5, 126.4, 64.5, 50.3, 49.0, 31.7, 26.2, 22.6, 20.6; MS (EIMS): $C_{20}H_{32}N_2$ (*m*/*z* 300).

4.3. (2*R*,3*R*,11*R*,12*R*)-*N*,*N*′,*N*″,*N*‴-Tetrakis-(2-propyl)-1,4,10,13-tetraaza-2,3;11,12-dibutano-6,9;15,17-dietheno-2*H*,3*H*,5*H*,9*H*,11*H*,12*H*,14*H*,18*H*-dodecahydro-(18)-annulene 6

Yield: 60% (0.4 g); Mp: 244–248 °C (with decomposition); $[\alpha]_D^{25} = -95.0$ (*c* 0.4, 1 M HCl); IR (KBr, cm^{-1}): 2962, 2932, 1464, 1167; ^{1}H NMR (400 MHz; (0 °C); $CDCl_3$) δ_H 8.03 (s, 2H), 7.06 (m, 2H), 6.98 (d, *J* = 6.8 Hz, 2H), 6.88 (m, 2H), 3.74 (d, *J* = 12.0 Hz, 2H), 3.49 (d, *J* = 12.0 Hz, 2H), 3.21 (septet, *J* = 6.0 Hz, 2H), 3.00 (d, *J* = 11.6 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.69–2.56 (m, 6H), 2.37 (d, *J* = 10.8 Hz, 2H), 1.80–1.78 (m, 6H), 1.65 (m, 2H), 1.42 (d, *J* = 6.0 Hz, 6H), 1.21–1.19 (m, 6H), 1.11 (d, *J* = 6.0 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 6H), 0.80 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 141.9, 139.6, 133.3, 128.8, 127.7, 125.8, 58.0, 48.4, 47.4, 45.4, 31.1, 26.9, 26.5, 23.9, 21.3, 19.7, 19.1; CHN calculated: C, 80.0; H, 10.6; N, 9.3; found: C, 79.9%; H, 10.9%; N, 8.9%; MS (FABMS): $C_{40}H_{64}N_4$ (*m*/*z* 601 M + 1).

4.4. (2*R*,3*R*,12*R*,13*R*)-*N*,*N*′,*N*″,*N*‴-Tetrakis-(2-propyl)-1,4,11,14-tetraaza-2,3;12,13-dibutano-6,9;16,19-dietheno-2*H*,3*H*,5*H*,10*H*,12*H*,13*H*,15*H*,20*H*-dodecahydro-(20)-annulene 7

Yield: 34% (0.2 g); Mp: 252 °C (decomposition), $[\alpha]_D^{25} = -20.5$ (*c* 0.3, CH_2Cl_2); IR (KBr, cm^{-1}): 2961, 2922, 1167; ^{1}H NMR (400 MHz; (−20 °C) $CDCl_3$) δ_H 6.98 (s, 8H), 3.58 (d, *J* = 13.6 Hz, 2H), 3.22 (d, *J* = 13.2 Hz, 2H), 3.20 (d, *J* = 14.8 Hz, 2H), 3.15 (septet, *J* = 6.4 Hz, 2H), 2.85 (d, *J* = 14.8 Hz, 2H), 2.84 (t, *J* = 8.8 Hz, 2H) 2.80 (septet, *J* = 6.8 Hz, 2H), 2.62 (t, *J* = 9.6 Hz, 2H), 2.26 (d, *J* = 12.0 Hz, 2H), 1.90–1.83 (m, 6H), 1.74–1.68 (m, 2H), 1.42 (d, *J* = 6.4 Hz, 6H), 1.28–1.14 (m, 6H), 1.10 (d, *J* = 6.4 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H), 0.86 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 139.7, 138.7, 129.0, 127.6, 60.1,

56.7, 49.0, 47.5, 45.5, 30.6, 28.2, 27.2, 26.6, 25.5, 21.8, 20.3, 18.9; CHN calculated: C, 80.0; H, 10.6; N, 9.3; found: C, 79.9%; H, 10.8%; N, 9.0%; MS (FABMS): $C_{40}H_{64}N_4$ (*m*/*z* 601, M + 1).

4.5. Polyamide-carboxylic acid 10

To a stirred solution of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **1** (0.5 g, 2.5 mmol) and triethyl amine (2 mL) in tetrahydrofuran (40 mL) was added adipoyl chloride (0.36 mL, 2.5 mmol) at 0 °C and the reaction mixture stirred for 12 h at 25 °C. The solids were filtered off and the solution extracted with ether (2×30 mL). The organic extracts were washed with 10% aq NaOH (2×20 mL) and brine (30 mL). The organic extracts were dried over Na_2SO_4 and the residue was evaporated to obtain polyamide **10**: yield: 0.6 g; $[\alpha]_D^{25} = -42.0$ (*c* 0.8, CH_2Cl_2); IR (neat, cm^{-1}): 3476, 2964, 2934, 1741, 1631; ^1H NMR (200 MHz; $CDCl_3$) δ_H 5.90 (br), 5.60 (br), 5.00 (br), 3.96 (br), 3.24 (br), 3.10 (d, $J = 6.8$ Hz), 2.99 (d, $J = 6.0$ Hz), 2.88 (m), 2.79 (d, $J = 7.0$ Hz), 2.64 (t, $J = 7.4$ Hz); GPC: $M_n = 27\,499$, $M_w = 30\,720$, (PDI = 1.11).

4.6. Polyamino alcohol 11[15]

To a suspension of $NaBH_4$ (0.42 g, 12 mmol) in tetrahydrofuran (75 mL) was added a solution of I_2 (1.4 g, 6 mmol) at 0 °C under a nitrogen atmosphere over 30 min. The polyamide (0.6 g) dissolved in THF (30 mL) was added to the generated diborane and refluxed for 12 h. The reaction was quenched with 1 N HCl. The mixture was neutralized with 1 M NaOH and the resultant amino alcohol extracted with ether. The organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and the residue evaporated to obtain polyamino alcohol **11**: yield: 0.3 g; $[\alpha]_D^{25} = -80.0$ (*c* 0.4, CH_2Cl_2); IR (neat, cm^{-1}): 3292, 2961, 2930; ^1H NMR (200 MHz; $CDCl_3$) δ_H 3.50 (t, $J = 6.4$ Hz), 2.90 (m), 2.75 (m), 2.33 (m), 1.93 (m), 1.64 (m), 0.95 (m).

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12. Mass spectral analysis of this mixture of products indicated the presence of higher macrocycles and oligomers. However, the eleven carbon signals observed in the ^{13}C NMR (100 MHz) spectrum for this product mixture at 140.9, 130.0, 127.5, 126.9, 59.8, 48.3, 46.4, 28.5, 26.6, 23.8 and 19.9 δ (ppm) and the absence of signals due to the anticipated end groups of the polymers indicate the product mixture contains macrocycles rather than polymers.
13. Crystal data for the macrocycle **6**: $C_{40}H_{64}N_4$, MW = 600, orthorhombic, space group I222, $a = 14.204$ (3) Å, $b = 16.717$ (3) Å, $c = 17.267$ (4) Å, $\beta = 90.00°$, $V = 4100.0$ (14) $Å^3$, $Z = 10$, $\rho_c = 1.217\,mg\,m^{-3}$, $\mu = 0.071\,mm^{-1}$, $T = 293$ K. Of the 3890 reflections collected 3890 were unique ($R_{int} = 0.0000$). Refinement on all data converged at $R_1 = 0.1075$, $wR_2 = 0.3058$. Crystallographic data for this structure has been deposited with Cambridge Crystallographic Data Centre, Deposition number CCDC 236325.
14. Crystal data for the macrocycle **7**: $C_{40}H_{64}N_4$, MW = 600, orthorhombic, space group $P\,21\,21\,21$, $a = 15.051$ (3) Å, $b = 16.556(3)$ Å, $c = 29.858$ (6) Å, $\beta = 90.00°$, $V = 9440(3)$ $Å^3$, $Z = 18$, $\rho_c = 1.207\,mg\,m^{-3}$, $\mu = 0.070\,mm^{-1}$, $T = 293$ K. Of the 9308 reflections collected, 9308 were unique ($R_{int} = 0.0000$). Refinement on all data converged at $R_1 = 0.0549$, $wR_2 = 0.1239$. Crystallographic data for this structure has been deposited with Cambridge Crystallographic Data Centre, Deposition number CCDC 236326.
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