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Chiral Macrocyclic Aliphatic Oligoimines Derived from *trans*-1,2-Diaminocyclohexane

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Abstract: Aliphatic dialdehydes of rigid structures having a cyclohexane, a bicyclo[2.2.2]octane or a [7]triangulane skeleton, have been condensed with enantiomerically pure *trans*-1,2-diaminocyclohexane to give [3+3] or [2+2] macrocyclization products. Unlike acyclic aliphatic imines, these macrocyclic oligoimines show enhanced stabilities and their structures in the crystals could be determined by X-ray diffraction analyses. The enantiomerically pure [7]triangulane dialdehyde showed remarkable diastereoselectivity in the condensation with the two enantiomers of *trans*-1,2-diaminocyclohexane: only one of the enantiomers gave a [2+2] macrocyclization product. Circular dichroism measurements combined with computational analysis show that the lowest energy electronic transition in these cyclic oligoimines is of n–π* type.

Keywords: circular dichroism · diastereoselectivity · imines · triangulanes · X-ray diffraction

Introduction

The imine bond is of paramount importance in organic chemistry and biochemistry, due to its ease of formation, its high reactivity and thereby versatility for further transformations.[1] The propensity of the imine bond to undergo further reactions usually follows the pattern of nucleophilicity of the amine component and the reactivity of the carbonyl precursor. Thus, it is generally accepted that Schiff bases obtained from at least one aromatic precursor are stable and less reactive than those formed from aliphatic carbonyl components.[2] Aliphatic imines are frequently poorly characterized and are used directly as intermediates in organic syntheses.

Oligomeric macrocyclic Schiff bases can often be readily assembled from aromatic dialdehydes and/or diamines,[3] provided that the steric constraints allow for the formation of a macrocycle. Due to geometrical constraints, planar macrocycles usually prefer a structure of a three- to six-membered regular polygon. Chiral macrocycles are apparently much less frequently encountered. For example, chiral triangular macrocycles **3** (see Scheme 1) were obtained in high yields by a [3+3] cyclocondensation of enantiomerically pure *trans*-1,2-diaminocyclohexane (DACH, **1**) and aromatic 1,4-dialdehydes **2**, such as terephthalaldehyde.[4]

These thermodynamically driven cyclocondensations, controlled by low-energy conformations of the substrates and the products, are remarkable examples of efficient, high-yielding, one-step assemblies of macrocycles,[5] which can eventually be reduced to the corresponding cyclic oligoamines.[6]

Various substituted trianglimines[7] have been obtained subsequently from DACH and linear aromatic dialdehydes.[8,9] Achiral triangular shape-persistent cyclocondensation products were prepared from 1,2-diaminobenzene and linear aromatic *ortho*-hydroxy dialdehydes.[10,11] Oligoimine macrocycles obtained from DACH can adopt structures

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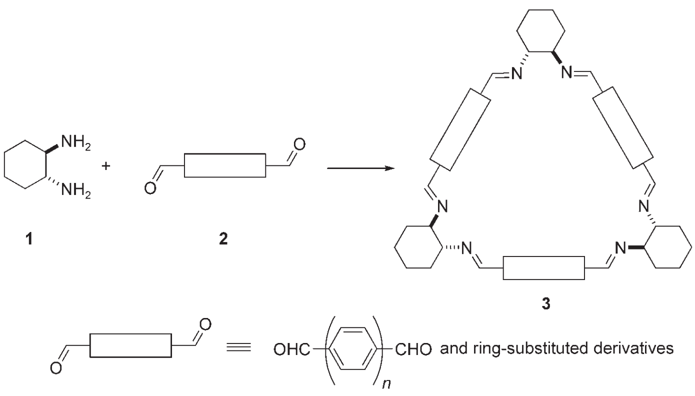


Scheme 1. Schematic representation of the syntheses of macrocyclic oligoimines **3**.

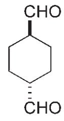
other than triangular, depending on the preferred conformation of the diamine and aromatic dialdehyde components. Among these, rhombimine[12] and loopimine[13] products have been characterized. We reasoned that the stability of all-aliphatic oligoimines could be enhanced by formation of a low-energy macrocyclic structure. We have chosen four cyclic aliphatic dialdehydes, **4**–**7**, two of them were of rigid linear type (**4**, **5**) whereas the remaining ones (**6**, **7**) possess a rigid [2]- (**6**) or [7]triangulane (**7**) skeleton with non-linear arrangement of the aldehyde groups. The latter two dialdehydes are chiral and therefore offer the opportunity to study the aspect of a potential diastereoselectivity of the oligoimination reactions. In addition, chirality of the oligoimine products could cause interesting chiroptical properties (electronic circular dichroism spectra) of this class of organic compounds, which have not previously been observed.

Results and Discussion

Synthesis of the precursors and macrocycles: The aliphatic dialdehydes required for the planned macrocyclization reactions are not available commercially. In general, they were obtained by Swern oxidation of the corresponding bis-hydroxymethyl precursors (see Supporting Information). *trans*-1,4-Cyclohexanedicarbaldehyde (**4**)[14] and bicyclo[2.2.2]octane-1,4-dicarbaldehyde (**5**)[15] as well as the synthetic access to the bishydroxymethyl precursor of [7]triangulanedialdehyde **7**[16] have been reported previously. Enantiomerically pure [1*R*,3*R*,4*S*)-spiropentane-1,4-dimethanol ([2]triangulanedimethanol) was prepared in five steps in 28 % overall yield starting from the known ([1*S*,3*R*)-4,4-dibromospiropent-1-yl]methanol.[16]

The diamine–dialdehyde cyclocondensation reactions were carried out in dichloromethane under inert atmosphere. In order to secure anhydrous conditions, molecular sieves 4 Å were added and the solutions were stirred at room temperature for 24 h. Typical concentrations of both diamine and dialdehyde substrates were 0.4 M. In the case of **5** and **1**, the reaction was carried out in cyclohexane and benzene in addition to a dichloromethane solution, and the product isolated in all cases was **9**. The crude products of the reactions between **1** and dialdehydes **4**, **5** and **7** were examined by ^{1}H NMR spectroscopy to show complete consumption of both substrates and disappearance of the aldehyde proton signals. According to the ^{1}H NMR spectra, only one cyclic product was formed in each case. The mass spectra indicated the formation of [3+3] cyclocondensation products **8** and **9** from dialdehydes **4** and **5**, whereas in the case of dialdehyde **7** the product of a [2+2] cyclocondensation (**10**) was obtained selectively. Crystals suitable for X-ray diffraction studies were grown by slow crystallization from methanol/ethyl acetate (**8**, **9**) or by slow evaporation of solvents from dichloromethane/cyclohexane in the case of **10**. It is remarkable that these aliphatic macrocyclic oligoimines **8**–**10** could be isolated as stable, crystalline compounds, a feature usually not associated with simple aliphatic imines. The strain-free macrocyclic environment in association with a certain degree of steric shielding apparently renders the imine groups less reactive in these cases.

With the chiral enantiomerically pure [7]triangulane dialdehyde **7** no selective cyclocondensation took place when the (*S*,*S*)-enantiomer of DACH (*ent*-**1**) was used. ^{1}H NMR and MS analysis of the crude product indicated a complex mixture of different components (presumably acyclic oligomers) from which no macrocyclic product could be isolated. Such a diastereoselectivity of cyclic oligoimine formation from chiral 1,2-diphenyl-1,2-diaminoethane and chiral 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dialdehyde had been demonstrated for the first time by Brunner et al.[17]



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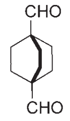

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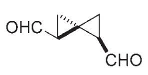

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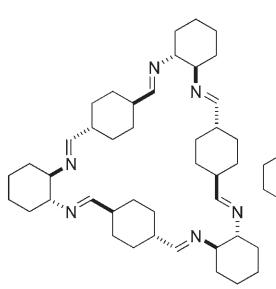

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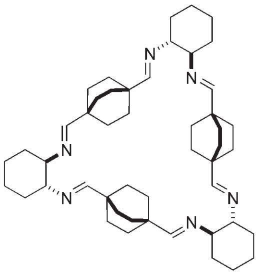

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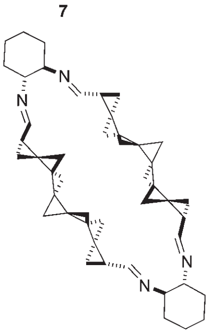
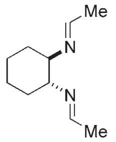


10

No selective formation of a macrocycle was found in the case of the chiral [2]triangulanedicarbaldehyde (**6**). Condensation of **6** with either enantiomer of **1** produced mixtures of oligoimines, including open-chain species, which could be identified by the presence of the formyl group signals in the ^{1}H NMR spectrum of the crude reaction mixture. Attempts to isolate any of the products by recrystallization failed.

For spectroscopic studies, diimine **11a** was prepared by condensation of dialdehyde **7** with cyclohexylamine in refluxing benzene, employing a Dean–Stark adapter. It is noteworthy that **11a** is quite unstable compared to the macrocyclic analogue **10**. Its ^{1}H NMR spectrum measured three hours after isolation showed the appearance of the formyl group signals.[18]

11a: R = Cy
11b: R = Me



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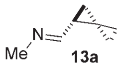
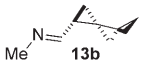
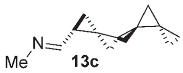


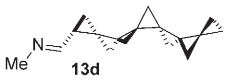
13a



13b



13c



13d

X-Ray diffraction studies: Formally asymmetric in the crystal, the molecules of **8** and **9** adopt a conformation that approximates C_3 symmetry. The space-filling drawings of the two molecules, presented in Figures 1a and 2a, illustrate that there is very little space inside the cavity of the molecule, and hence no potential for molecular inclusion. The two molecules are very similar in shape and dimensions. The closest interatomic distances in the molecular interior range from 3.939 to 4.625 Å in **8**, and from 3.735 to 4.386 Å in **9**. The external dimensions of trianglimines are also very similar in **8** and **9** and amount to 17.990 and 17.568 Å for the base and 15.317 and 15.263 Å for the height of the triangle, respectively. The quoted values are comparable to those observed in trianglimines with aromatic spacers (17.753 and 15.220 Å, respectively).[4] Although very similar in molecular topology, the two trianglimines display very different crystal architectures. Molecules of **9** pack in (100) layers (Figure 2b). The molecules in a consecutive layer are shifted and oriented antiparallel with respect to the reference layer (Figure 2c). Unlike molecules **9**, molecules **8** are arranged in stacks roughly parallel to the *b* direction (Figure 1b). The angle between the *b* direction and the direction of the stack amounts to 27.9°. Consequently, the stacks that are related by the two-fold screw axis parallel to *b* are inclined with respect to each other at an angle of 55.7° (the angle between normals to the planes defined by six nitrogen atoms constituting the triangle). The two sets of stacks propagate through the crystal forming a grid structure (Figure 1c). Nearly the same type of grid motif, with an inclination angle of 59.6°, is present in the crystal structure of the trianglimine with the aromatic 1,4-phenylene spacer,[4a] in spite of the fact that the latter crystal displays inclusion

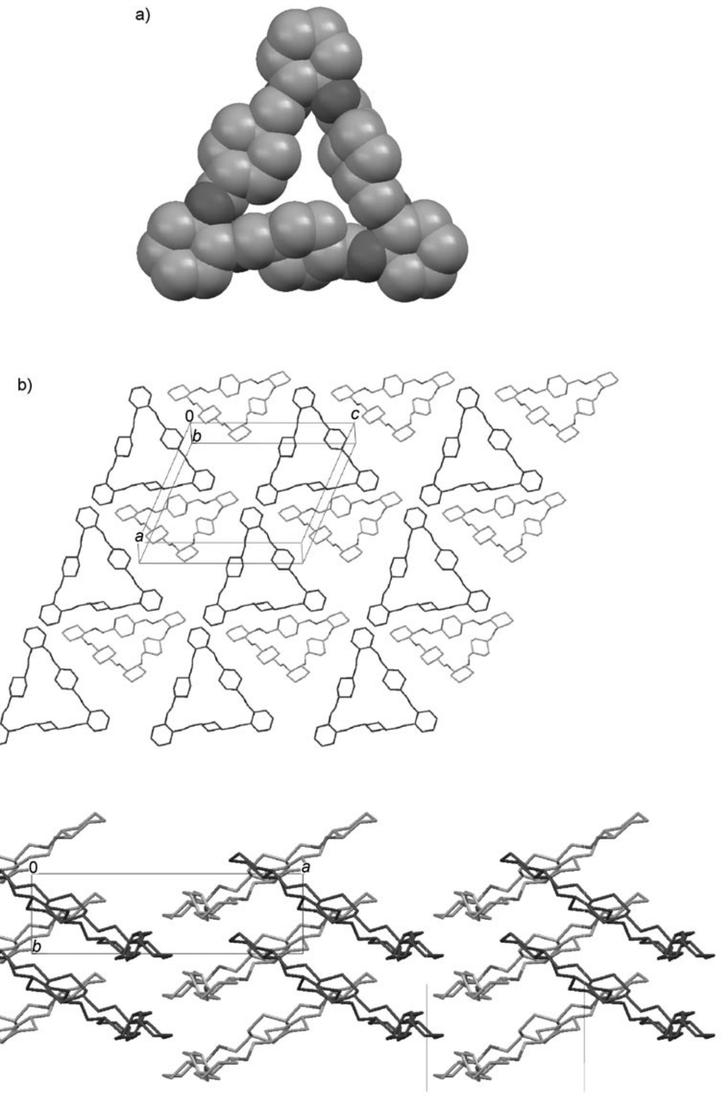


Figure 1. a) Space-filling representation of trianglimine **8**; b) top view of the stacks of molecules in the crystal; c) grid-like arrangement of neighboring stacks, as viewed along the *c* direction. In all the figures the hydrogen atoms have been omitted for clarity.

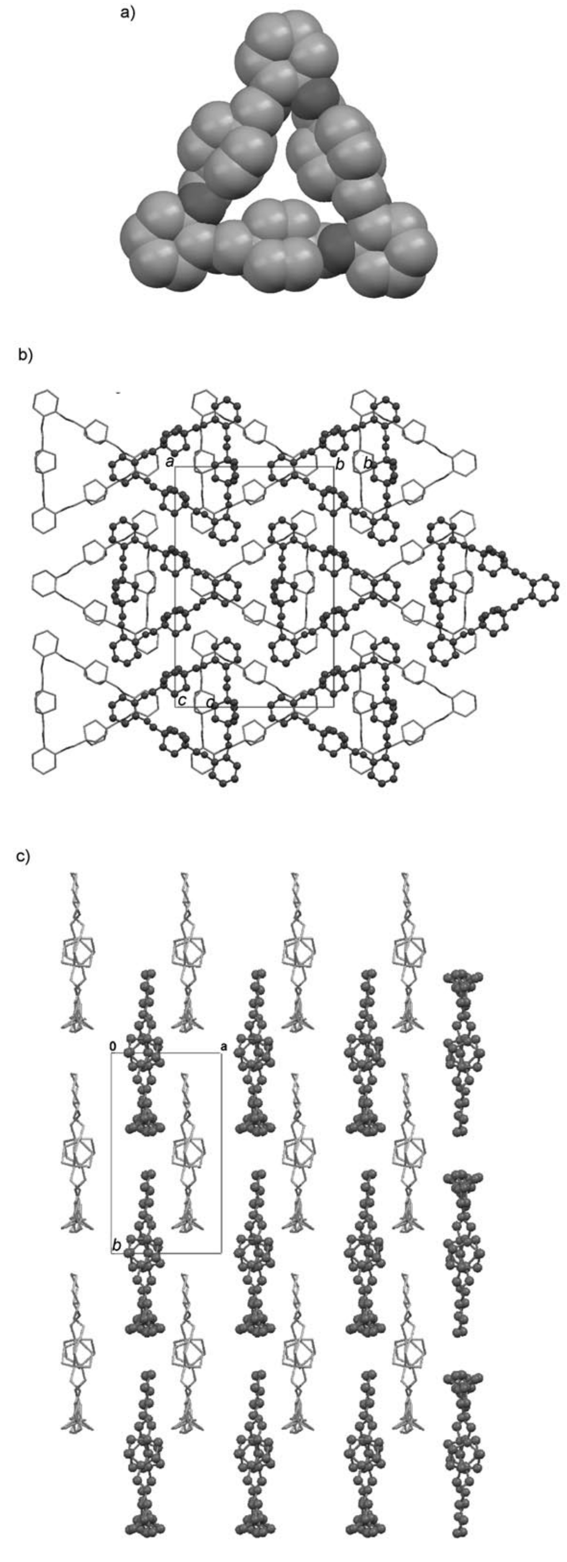


Figure 2. a) Space-filling representation of trianglimine **9**; b) view down the *a* axis showing a layered crystal structure of **9**. Two consecutive (100) layers are differentiated by wireframe and ball-and-stick representation of the molecules; c) side view of the (100) layers. In all the figures the hydrogen atoms have been omitted for clarity.

properties. Comparison of the crystal densities indicates that trianglimines in layered crystals pack less densely than trianglimines arranged in stacks (1.092 vs 1.120 $\mathrm{mg\,m^{-3}}$ of **9** and **8**, respectively).

Molecule **10**, shown in Figure 3a, consists of two helical chains composed of seven spiroannelated cyclopropane rings as the sides, and cyclohexane fragments as the apexes. Formally D_2 symmetric, the molecules crystallize in a trigonal system, space group $P3_12$ exposing only C_2 symmetry. The unit cell contains six molecules generated from two independent molecular halves, which occupy special sites [in Wyckoff notation[19] **10a** (molecule numbered C1 to C23) and **10b** (molecule numbered C25 to C48)]. In the former molecule the two-fold axis is perpendicular to the average molecular plane, while in the latter the two-fold axis lies in the average molecular plane and passes through atoms C39 and C48, which constitute the apexes of the cyclopropane rings situated in the middle of the linear fragments of spiroannelated cyclopropanes. Despite this difference, the molecules are very similar in shape; therefore only one of the two independent molecules has been depicted in Figure 3a. In both molecules, each of the two linear fragments consisting of spiroannelated cyclopropanes displays M (minus) helicity. The molecules in the crystal are oriented parallel (molecule C1 to C23) or nearly parallel (molecule C25 to C48) to the 3_1 screw axis; the angle between the c direction and the line passing through the middle of the cyclohexane C1−C2/C1a−C2a, and C25−C26/C25a−C26a bonds amounts to 0.3 and 18.8°, respectively. The nearly parallel orientation of molecules with respect to the three-fold screw axis gives rise to double helical columns of molecules that propagate along the c direction (Figure 3b). The disordered methylene chloride solvent molecules, located in crystal voids, one in a general and the other one in a special position, propagate along the same c direction as dictated by the 3_1 screw axis (Figure 3c).

Unlike trianglimines and trianglamines with aromatic spacers, the newly synthesized trianglimines with aliphatic spacers do not exhibit any inclusion properties. The molecules pack either in parallel layers or form a grid-like crystal structure. The cyclic tetraimines with helical [7]triangulane spacers form cigar-shaped macrocycles are arranged in the crystal lattice in a double helical manner with a supramolecular helicity sense opposite to that of the individual macrocycles.

Stereochemical considerations: The success or failure of oligoimine macrocyclization can be traced to predisposition of the substrates to form a strain-free cyclic structure. Thus, it is expected that the preferred skeleton conformation of a dialdehyde and a diamine is not changed significantly by forming the imine bonds in the reaction product.

In dialdehyde **4**, the directions of the C−CHO bonds are parallel (the formyl groups occupy equatorial positions) whereas in dialdehyde **5** the C−CHO bonds are colinear. The dihedral angles for (O)C-C···C-C(O) are 180 and 0°, respectively (Table 1). The corresponding dihedral angle

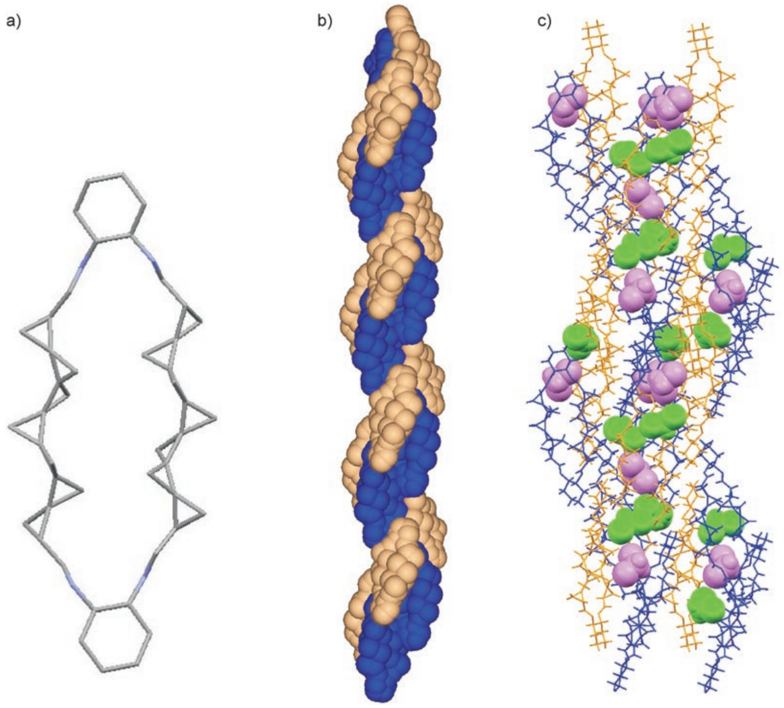


Figure 3. a) One of the two crystallographically independent molecules of **10**. Each of the two molecules utilizes the C_2 symmetry in the crystal, but in one case the two-fold axis is perpendicular while in the other parallel to the molecular best plane; b) double-helical arrangement of two independent molecules of **10** around the 3_1 screw axis (space-filling representation); c) part of the crystal structure of **10** displaying CH_2Cl_2 solvent molecules as van der Waals spheres.

values for O=C···C=O in dialdehydes, calculated at the DFT B3LYP/6-31g(d) level, are close to 180° (*anti*).

Such an arrangement favors the formation of the trianglimine macrocycle in the reaction with **1**, as it was also amply demonstrated in the reaction of **1** with aromatic dialdehydes.[4,7–9] In the current study, the aliphatic trianglimine products **8** and **9** were obtained selectively. The dihedral angle values N=C···C=N in the macrocycles **8** and **9** are smaller than 180°, according to both X-ray diffraction and computational (PM3 level) results, yet still in the majority of cases they fall in the range of an *anti* arrangement. Of interest are significant deviations from colinearity of the C–CH(N) bonds attached to the bicyclo[2.2.2]octane skeleton in macrocycle **9**. These data, obtained from both the X-ray crystal structure analysis and the PM3 semiempirical calculations (Table 1) indicate that steric interactions in the macrocycle **9** lead to a distortion of the bicyclo[2.2.2]octane skeleton, which otherwise must be considered as a rigid structure.

An important structural difference between the dialdehyde **4** and its aromatic analogue—terephthalaldehyde—is in the orientation of the formyl groups with regard to the ring. Whereas in terephthalaldehyde the formyl groups are approximately coplanar with the benzene ring,[4a] in dialdehyde **4** the formyl groups lie in a plane approximately perpendicular to the mean plane of the cyclohexane ring, that is, the H-C-C=N bonds resulting from the condensation are *syn* (Figure 4).

Note a general feature of the imine bonding between the two alicyclic moieties: *syn* arrangements of the C_{amine}H and the C_{imine}H, as well as the N=C–$C_{aldehyde}$H bonds is preferred in the lowest energy conformers, according to both PM3 and DFT level calculations.

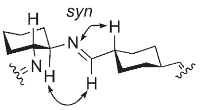


Figure 4. Preferred conformation of the cyclohexane ring-substituted imines on the basis of PM3 calculations and X-ray diffraction data.

In dialdehyde **7**, the dihedral angle O=C···C=O is positive (162°) in the lowest-energy conformation and the tetraimine macrocycle **10** can be formed only with (*R*,*R*)-**1**, in which the torsional angle N-C-C-N is negative (ca. −60°). In the case of (*S*,*S*)-**1**, both angles in the reacting molecules have positive values and such a combination makes the formation of a macrocycle unfavorable. Note that the dihedral angles N=C···C=N and (N)C-C···C-C(N) in the macrocycle **10**, either calculated or determined by X-ray diffraction, have the same sign and

Table 1. Dihedral angles characterizing the structures of dialdehydes **4–7** and oligoimine macrocycles **8–10**.

Aldehyde	Angle [°]		Imine	Angle [°]	
	O=C···C=O	(O)C-C···C-C(O)		N=C···C=N	(N)C-C···C-C(N)
4	180[a]	180[a]	**8**	−174, −175, −145[b,c] −179[d,e]	−178, −178, 176[b,c] 179[d,e]
5	180[a]	0[a]	**9**	157, 177, −169[b,c] −152[d,g]	122, −62, −77[b,c] −159[d,g]
6	60[a]	89[a]			
7	162[a]	−33[a]	**10**	131[b,f,i]; 136, 143[b,f,i] 135[f,h,i]; 133[f,h,i]	−42[b,f,i]; −23, −25[b,f,i] −34[f,h,i]; −32[f,h,i]

[a] The lowest-energy conformer calculated at B3LYP/6-31G* level. [b] X-ray. [c] C_1 symmetry. [d] Calculated at PM3 semiempirical level. [e] D_3 symmetry. [f] C_2 symmetry. [g] C_3 symmetry. [h] Calculated at B3LYP/6-31G* level. [i] Two independent molecules.

their magnitudes are comparable to the values of the corresponding dihedral angles O=C···C=O and (O)C-C···C-C(O) in the parent dialdehyde **7**. This is an indication that the formation of the [2+2] cyclocondensation product **10** is a thermodynamically favored process.

[2]Triangulanedicarbaldehyde **6** is a unique molecule in which the two (O)C−C bonds are at a right angle. The directions of the C=O bonds form an acute angle (60°) in the low-energy conformer (Table 1). The highly bent structure of the dialdehyde **6** is different from that of **4**, **5** and **7** and it apparently precludes the formation of a strain-free macrocycle in the condensation reaction with either enantiomer of diamine **1**.

In general it appears that the preferred structures of dialdehydes for the formation of imine macrocycles with DACH are those in which the O=C···C=O angle is larger than 120°. Small angles, as in dialdehyde **6**, make the formation of a macrocycle highly unfavorable. A significant diastereoselectivity of macrocycle formation may be observed as in the case of chiral [7]triangulanedialdehyde **7** and two enantiomers of diamine **1**.

Circular dichroism studies: The well-defined, chiral, all-aliphatic oligoimines **8**–**10** provide a unique opportunity to study their chiroptical properties. In particular, it should be possible to observe the low-lying n–π* transition of the imine chromophore in the CD spectra. In aromatic imines this transition is buried under the absorption envelope due to the transitions of the aromatic chromophore.

The weak absorption due to the imine n–π* transition is located around 240 nm. Indeed, the macrocyclic imines **8**–**10** display strong Cotton effects in their CD spectra. Hexaimines **8** and **9**, in which the chiral part is derived from the amine (DACH), display negative Cotton effects, $\Delta\varepsilon$ −3.5 (236 nm) for **8** and $\Delta\varepsilon$ −12.9 (239 nm) for **9** (Figure 5).

Furthermore, a negative Cotton effect was calculated (B3LYP/6-311G++(2d,2p)) for the model diimine **12**. The calculations show that the CD band located around 240 nm is in fact composed of several transitions involving the imine bond and contributing rotatory power of either positive or negative sign. On the other hand, the tetraimine **10** is characterized by a positive n–π* Cotton effect, $\Delta\varepsilon$ +46.0 at 239 nm. A positive n–π* Cotton effect was also calculated for the model diimine **11b**.[18] From the comparison of the CD data for **8**–**10** it is quite obvious that the dominating contribution to the net positive n–π* Cotton effect of **10** can be ascribed to the chiral [7]triangulane skeleton. This contribution apparently overrides a negative contribution of the (*R*,*R*)-1,2-disubstituted cyclohexane skeleton which is demonstrated by a negative n–π* Cotton effect of **8** and **9**. The effect of an [*n*]triangulane skeleton can also be traced by the calculated CD spectra of the series of homochiral triangulane monoimines **13a**–**d** (Figure 6). In all these cases, the calculated n–π* Cotton effect was found positive, with the intensity increasing in the order of adding the cyclopropane structural motif (n=2, 3, 5, 7).

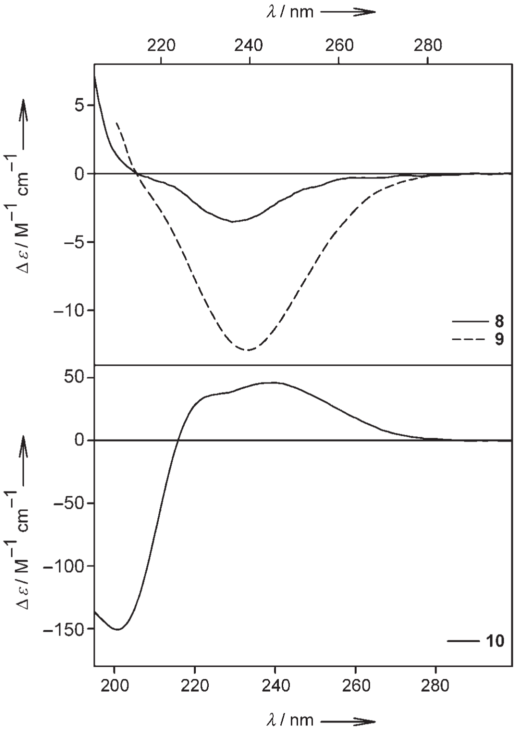


Figure 5. Experimental CD spectra (in acetonitrile/5 % methanol) of triangular macrocyclic hexaimines **8** and **9** (upper panel) and macrocyclic tetraimine **10** (lower panel).

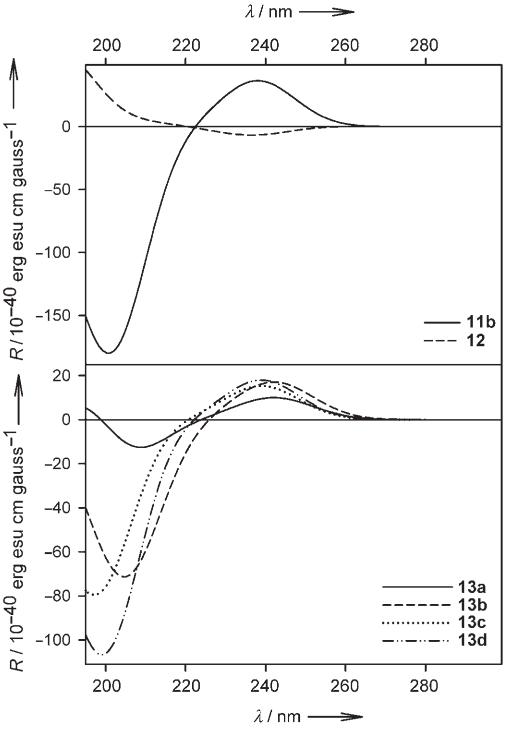


Figure 6. Calculated (at the B3LYP/6-311++g(2d,2p) level) CD spectra of model diimines **11b** and **12** (upper panel) and model monoimines **13a**–**13d** (lower panel).

Conclusions

Aliphatic imines are considered highly reactive and unstable species. The present work shows that imine reactivity and stability can be significantly altered by the inclusion in a strain-free macrocyclic ring. Such macrocyclic oligoimines are readily obtained by cyclocondensation of enantiomerically pure *trans*-1,2-diaminocyclohexane with aliphatic dialdehydes of rigid skeletons. Two of the dialdehydes, with a 1,4-disubstituted cyclohexane or [2.2.2]bicyclooctane skeleton, formed near perfectly symmetrical triangular hexaimines (trianglimines) whereas the dialdehyde having a [7]triangulane skeleton gave a cigar-shaped [2+2] cyclocondensation product predominantly. It appears that successful cyclocondensations are possible with dialdehydes having the formyl groups in (approximately) colinear arrangement. Dialdehydes with the C–CHO bonds forming an obtuse dihedral angle are not structurally suited to form macrocyclic structures with *trans*-1,2-diaminocyclohexane selectively. Furthermore, diastereoselectivity of the macrocycle versus linear oligomer formation was observed when both the diamine and the dialdehyde were chiral. The model of the lowest energy conformation of the all-aliphatic imine bond has been deduced from semiempirical calculations and X-ray diffraction studies.

The chiral aliphatic macrocyclic oligoimines obtained in this study provided a unique opportunity to observe in the circular dichroism spectra the Cotton effect which is associated with the lowest energy n–π* type electronic transition of the imine chromophore.

We anticipate that stabilization of highly reactive aliphatic imine by its incorporation into macrocyclic structure, as described here, will find further applications in synthetic and structural chemistry.

Experimental

General information: ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ solution. Chemical shifts (δ) are reported in ppm relative to $SiMe_4$ and coupling constants (J) are given in Hz. Mass spectra were recorded using the FAB method (NBA matrix). UV and CD spectra were recorded in acetonitrile/methanol solutions, unless stated otherwise.

For computational details see Supporting Information.

General procedure for the synthesis of oligoimines from *trans*-(1*R*,2*R*)-diaminocyclohexane and aliphatic dialdehydes: To a solution of **1** (114 mg, 1 mmol) in dichloromethane (1.5 mL), containing molecular sieves 4 Å (150 mg), an equimolar solution of the respective dialdehyde in dichloromethane (1 mL) was added slowly with a syringe. The mixture was stirred at room temperature under argon atmosphere overnight. After filtration and evaporation of the solvent, the crude product was crystallized whenever possible.

Macrocycle 8: yield: 213 mg (97 %, crude isolated product); 39 % after recrystallization; m.p. > 320 °C (methanol/ethyl acetate); $[\alpha]_D^{20}=81$ ($c=0.6$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.34$ (d, ^3J(H,H) = 6.6 Hz, 6H; CH=N), 2.98–2.95 (m, 6H; CHN=), 2.04 (brs, 6H), 1.81–1.62 (m, 30H), 1.37–1.18 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta=168.7$ (*C*H=N), 79.4, 43.2, 32.9, 29.3, 28.5, 24.4 ppm (-*C*H$_2$-); IR (KBr): $\tilde{\nu}=1665$ cm^{-1}; UV (acetonitrile/methanol 9:1): λ_{max} (ε) = 239 (620 mol^{-1}dm^{3}cm^{-1}); CD (acetonitrile/methanol 9:1) λ_{max} ($\Delta\varepsilon$) = 236 (−3.5 mol^{-1}dm^{3}cm^{-1}); HRMS (FAB, NBA): *m*/*z*: calcd for $C_{42}H_{67}N_6$: 655.5427; found: 655.5405 $[M+H]^+$.

Macrocycle 9: yield: 230 mg (94 %, crude isolated product); yield: 43 % after recrystallization; m.p. > 320 °C °C (methanol/ethyl acetate); $[\alpha]_D^{20}=72$ ($c=0.55$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.43$ (s, 6H; HC=N), 2.98–2.96 (m, 6H; CHN), 1.75–1.73 (m, 6H; CH_2), 1.56 (brs, 48H; CH_2), 1.35–1.34 ppm (m, 6H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta=170.6$ (*C*=N), 74.1, 36.7, 32.8, 29.1, 28.4, 24.4 ppm (-*C*H$_2$-); IR (KBr): $\tilde{\nu}=1663$ cm^{-1}; UV/Vis (acetonitrile/methanol 9:1): λ_{max} (ε) = 234 (880 mol^{-1}dm^{3}cm^{-1}); CD (acetonitrile/methanol 9:1) λ_{max} ($\Delta\varepsilon$) = 239 (−12.9 mol^{-1}dm^{3}cm^{-1}); HRMS (FAB, NBA): *m*/*z*: calcd for $C_{48}H_{73}N_6$: 733.5897; found: 733.5871 $[M+H]^+$.

Macrocycle 10: yield: 309 mg (93 %, crude isolated product); 32 % after recrystallization; m.p. > 280 °C (dichloromethane/cyclohexane); $[\alpha]_D^{20}=-401$ ($c=0.65$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.15$ (d, ^3J(H,H) = 6.6 Hz, 4H; CH=N), 3.10–3.03 (m, 4H; CHN=), 1.85–1.59 (m, 16H), 1.39–1.32 (m, 8H), 1.17–1.11 (m, 20H), 1.0 ppm (d, ^3J(H,H) = 4.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta=165.4$ (*C*H=N), 72.8, 53.4, 33.7, 24.4, 22.7, 19.4, 17.7, 17.1, 12.1, 10.6, 9.6, 8.8 ppm; IR (KBr): $\tilde{\nu}=1658$ cm^{-1}; CD (acetonitrile/methanol 95:5) λ_{max} ($\Delta\varepsilon$) = 239 (46.0), 201 (−150.7 mol^{-1}dm^{3}cm^{-1}); HRMS (FAB, NBA): *m*/*z*: calcd for $C_{46}H_{57}N_4$: 665.4583; found: 665.4589 $[M+H]^+$.

Attempted macrocyclization with the use of aldehyde **6**, according to the above described procedure, failed to produce any isolable macrocycle. The ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of both the aldehyde and the C–H(amine) signals.

X-ray structure determination of compounds 8–10: Trianglimine with a cyclohexane spacer (**8**) was recrystallized from ethyl acetate/methanol 1:1 with a few drops of methylene chloride with the formula $C_{42}H_{66}N_6$, $M_r=655.01$, $T=150$ K. Crystal system: monoclinic. Space group: $P2_1$. Unit cell dimensions: $a=18.857(4)$, $b=5.230(1)$, $c=20.925(4)$ Å; $V=1943.1(8)$ Å^3; $Z=2$; $\rho_{calcd}=1.120$ mg m^{-3}; Mo$_{K\alpha}$ ($\lambda=0.71073$, ω scan); $\mu=0.066$ mm^{-1}. Final R value 0.062 for 3176 observed reflections $[I>2\sigma(I)]$. Crystal size: 0.6 × 0.1 × 0.05 mm. Data was collected with a KM4CCD kappa-geometry diffractometer[20] equipped with graphite monochromator. Theta range for data collection was 2.92 to 25.07°. Of the 16309 reflections collected, 3855 were unique ($R_{int}=0.077$) and 3176 were considered as observed with $I>2\sigma(I)$. The intensity data were corrected for Lp effects. No absorption correction was applied.

Trianglimine with a bicyclo[2.2.2]octane spacer (**9**) was recrystallized from ethyl acetate/methanol 1:1 with a few drops of methylene chloride with the formula $C_{48}H_{72}N_6$, $M_r=733.12$, $T=295.9(0$ K. Crystal system: orthorhombic. Space group: $P2_12_12_1$. Unit cell dimensions: $a=9.611(2)$, $b=17.498(3)$, $c=26.508(5)$ Å; $V=4457.9(2)$ Å^3; $Z=4$; $\rho_{calcd}=1.092$ mg m^{-3}; Mo$_{K\alpha}$ ($\lambda=0.71073$, ω scan); $\mu=0.064$ mm^{-1}. Final R value 0.051 for 3772 observed reflections $[I>2\sigma(I)]$. Crystal size: 0.6 × 0.45 × 0.2 mm. Data was collected with a KM4CCD kappa-geometry diffractometer[20] equipped with graphite monochromator. Theta range for data collection was 3.07 to 26.07°. Of the 25426 reflections collected, 4910 were unique ($R_{int}=0.032$) and 3772 were considered as observed with $I>2\sigma(I)$. The intensity data were corrected for Lp effects. No absorption correction was applied.

Cyclic tetraimine with a triangulane spacer (**10**) was recrystallized from methylene chloride and a few drops of cyclohexane as an inclusion compound with the formula $C_{46}H_{56}N_4 \times 1.2(CH_2Cl_2)$, $M_r=766.9$, $T=150$ K. Crystal system: trigonal. Space group: $P3_121$. Unit cell dimensions: $a=14.724(2)$ $c=35.376(7)$ Å; $V=6641.9(2)$ Å^3; $Z=6$; $\rho_{calcd}=1.150$ mg m^{-3}; Mo$_{K\alpha}$ ($\lambda=0.71073$, ω scan); $\mu=0.206$ mm^{-1}. Final R value 0.052 for 6344 observed reflections $[I>2\sigma(I)]$. Crystal size: 0.4 × 0.2 × 0.15 mm. Data was collected with a KM4CCD kappa-geometry diffractometer[20] equipped with graphite monochromator. Theta range for data collection was 3.46 to 25.03°. Of the 52768 reflections collected, 7828 were unique ($R_{int}=0.053$) and 6344 were considered as observed with $I>2\sigma(I)$. The intensity data were corrected for Lp effects. No absorption correction was applied. Macrocycle **10** crystallized with methylene chloride solvent molecules in a 1:1.2 ratio, with one molecule occupying a general, and the other a special position site, with an occupancy of 0.8. In order to account for the contribution of solvent molecules to the diffraction intensities, we assumed the presence of orientational disorder of both molecules which describes rotation around one of the two C–Cl bonds. For the molecules in a general position we included two overlapping instances for the Cl2 atom with occupancy factors of 0.52 and 0.28; for the molecule in a special position both overlapping instances for Cl3 refined with an occupancy factor of 0.4.

Data reduction and analysis for all structures were carried out with the CrysAlisRED.[21] The structures were solved by direct methods using SHELXS97[22,23] and refined by the full matrix least-squares technique with SHELXL97.[23] Non-hydrogen atoms were refined anisotropically. The positions of all H atoms attached to carbon atoms were calculated geometrically (C–H = 0.96 Å). All H-atoms were refined using a riding model and their isotropic displacement parameters were given a value 20% higher than the isotropic equivalent for the atom to which the H atoms were attached. The absolute structure of the crystals was assumed from the known absolute configuration of (*R*,*R*)-*trans*-1,2-diaminocyclohexane used in the synthesis. A Mercury program was used to prepare the drawings.[24]

CCDC-638026 (**8**), -638025 (**9**) and -638027 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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