# Designing Large Triangular Chiral Macrocycles: Efficient [3 + 3] Diamine−Dialdehyde Condensations Based on Conformational Bias

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Triangular 30- and 27-membered hexaiminomacrocycles **4** and **5** of $D_3$ and $C_3$ symmetry, respectively, are readily obtained by unprecedented [3 + 3] cyclocondensation of (*R*,*R*)-1,2-diaminocyclohexane with, accordingly, terephthalaldehyde and isophthalaldehyde. The course of the reaction, leading to macrocyclization, is governed by conformational constraints imposed on the structural components of the intermediate products, as shown by molecular modeling. X-ray analysis of cocrystal **4·AcOEt** revealed that the macrocycle symmetry significantly departs from ideal $D_3$ symmetry due to crystal environment. Cyclic hexaamines **6** and **7** were prepared by sodium borohydride reduction of **4** and **5**, respectively.

## Introduction

Despite current interest, macrocyclic molecules with rings larger than 20 atoms are less frequently encountered than their smaller-ring counterparts.[1,2] In the case of polyazamacrocycles, standard synthetic method is based on a high-dilution ring formation from aliphatic diamines and aromatic dialdehydes via the Schiff bases[3] or from aliphatic diamines and dicarboxylic acids dichlorides via the cyclic diamides.[4] Alternatively, the cation templating effect is used to direct the oligomerization reaction, as in the case of [2 + 2] cyclocondensation of 1,2-diaminobenzene with pyridine 2,6-dicarboxaldehyde.[5]

A well-documented example of an efficient self-assembly of the multicyclic compound is the synthesis of hexamethylenetetramine from ammonia and formaldehyde. This reaction is believed to proceed through a diimine intermediate and is directed by the ability of the chairlike six-membered rings to form an adamantane-like structure.[6] A classical example of preferential formation of a 12-membered heterocycle over the open-chain oligomers is based on the conformational effect of the bulky *N*-tosyl substituents in the diamine component.[7]

Recently (1*R*,2*R*)-1,2-diaminocyclohexane (**1**) has been extensively used for the synthesis of chiral diimine ligands with variety aromatic aldehydes. These ligands are efficient in catalytic asymmetric epoxidation,[8] aziridination,[9] nucleophilic epoxide ring opening,[10] Michael addition,[11] the Diels−Alder reaction,[12] cyanide addition to aldehydes[13] and imines[14] (Jacobson catalysts), as well as in the construction of supramolecular structures[15] and molecular receptors.[16]

We envisaged that **1**, featuring a rigid structure and equatorial amino substituents, would facilitate ring formation in the reaction with aromatic dialdehydes, such as terephthalaldehyde (**2**) and isophthalaldehyde (**3**), whose molecules are essentially planar. The two C−N bonds in **1** are projected at 60° angle from the center of the cyclohexane ring and hence macrocycle formation is anticipated to proceed through a [3 + 3] diamine-

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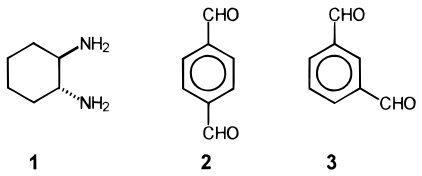
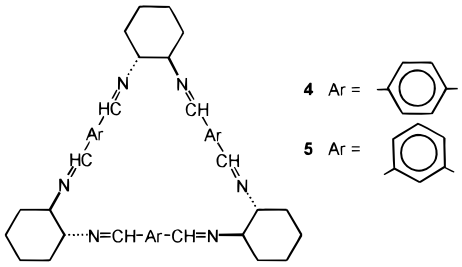
dialdehyde addition, with molecules **1** placed at each vertex of a regular triangle in the final product.




**1** **2** **3**

## Results and Discussion

**Synthesis.** To test this hypothesis we subjected diamine **1** to Schiff base formation with dialdehyde **2** under variety of conditions (e.g., in refluxing benzene or at room temperature in dichloromethane). The typical concentration of each of the reactants was 0.4 M. The product isolated in all cases was **4**, even when the stoichiometry of **1** to **2** was different from one to one. The reaction was also followed by $^1$H NMR in 0.1 M solution in $CDCl_3$ at 24 °C. Upon mixing of the reactants, rapid disappearance of the CHN multiplet of **1** at 2.25 ppm and appearance of the transient multiplet at 2.95 ppm was observed, the latter evetually converging to a multiplet at 3.4 ppm due to the CHN signal in **4**. The conversion of the aldehyde signal of **2** at 10.15 ppm to the imine signal of **4** at 8.15 ppm with transient formation of the signals of the intermediate products could also be observed. Within 2 h, less than 5% of substrates **1** and **2** could be detected by NMR, even though no water was removed from the reaction medium.

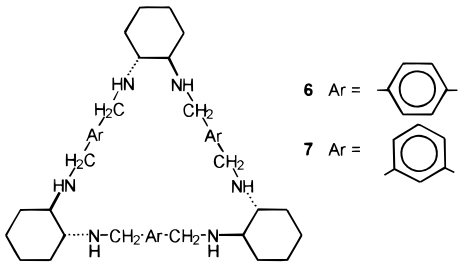



Structure determination of **4** was straightforward. The MS gave molecular ion, $m/z = 636$, corresponding to the trimeric structure $(C_{14}H_{16}N_2)_3$. The $^1$H NMR spectrum consisted of two sharp singlets at $\delta = 8.14$ and 7.52 corresponding to the resonances of the azomethine and the aromatic protons, respectively, as well as three multiplets, $\delta = 3.37$, 1.80, and 1.48, due to the cyclohexane resonances. Accordingly, the $^{13}$C NMR spectrum was made up of six peaks. These resonance signals are fully compatible with the $D_3$ symmetry structure. The IR spectrum displayed strong band of $\nu$ C=N at 1642 cm$^{-1}$. When crystallized from ethyl acetate, **4** formed a 1:1 inclusion compound with the solvent, as indicated by the $^1$H NMR and the IR spectral data.

Similarly, **1** was reacted with dialdehyde **3** to give the trimeric product **5** in high yield, whose structure was determined analogously to that of **4**. Notably different were the broadened signals of the $^1$H and $^{13}$C at C4/C6 positions of the aromatic ring in the NMR spectra measured at 20 °C (see below).

To the best of our knowledge, no [3 + 3] cyclocondensation of a dialdehyde with a diamine has been reported. It is of interest to note that none defined cyclic product could be obtained from the reaction of **1** with phthalaldehyde or from *rac*-**1** and **2**. Diamine **1** is known to undergo [1 + 1] cyclocondensation with a phenanthroline-based polycyclic aromatic dialdehyde,[17] as well as [2 + 2] cyclocondensation with 2,6-pyridinedicarboxaldehyde in the presence of barium dichloride template.[18]

The macrocyclic hexaimines **4** and **5** were readily reduced with sodium borohydride to macrocyclic hexaamines **6** and **7**,[19] whose trimeric structures were fully compatible with the recorded spectra (see the Experimental Section).




**Stereochemistry: Formation and Structure.** To elucidate the structural bias favoring the formation of the triangular products **4** and **5** we carried out MMX molecular modeling of the ground-state conformations of the products (**4**, **5**) as well as of some model intermediate molecules **8**−**13**.[20] The stereostructure of **4** was also studied with the X-ray crystal structure analysis and both **4** and **5** with the CD spectra and the variable-temperature NMR.

The synthesis of **4** can be envisaged as a stepwise formation of the imine bonds in the reaction of **1** and **2**. Since the structure of **1** is rigid, with the nitrogen substituents occupying the equatorial positions, the structures of the model intermediate products, such as **12** and **13**, are determined by the rotational freedom of the C−N bonds, connecting the cyclohexane and the aromatic rings. We further assumed, following the generally recognized notion, the *E* configuration of the C=N bonds. In addition, the conjugated N=C-aryl-C=N structural units were considered planar, in all possible conformational isomers resulting from the changes in the relative orientation of the imine bonds. Therefore, the imine conformers could be simply defined with the aid of the torsional angle H−C−N=C, $\omega$, as syn or anti (Scheme 1).

MMX molecular modeling indicates a preference for the syn conformer[21] **8a** of *N*-benzylidenecyclohexylamine over the anti conformer **8b**. Steric energy difference ($\Delta$SE) between the syn and the anti conformers is small, but it is consistently repeated in all further MMX calculations. Indeed, an SE preference of 1.8 and 2.5 kcal·mol$^{-1}$ is calculated for the syn conformers of diimines **9** and **10** derived from terephthalaldehyde (**9**) and isophthaldehyde (**10**), respectively, over their anti counterparts (Scheme 2). For this reason, the anti conformers were not included

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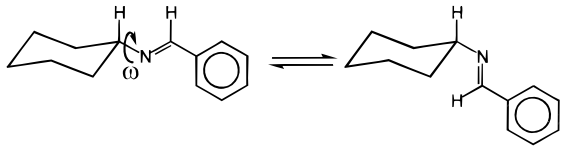
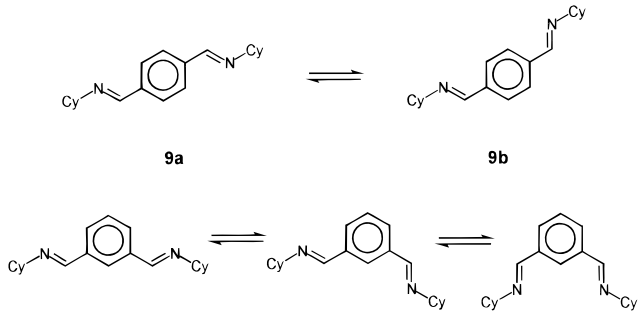
**Scheme 1**



**8a** *(syn)* **8b** *(anti)*

| | | |
|---|---|---|
| ω(H-C-N=C) [deg] | 0 | 180 |
| ΔSE [kcal/mol] | 0 | 0.92 |

**Scheme 2**



**9a** **9b**

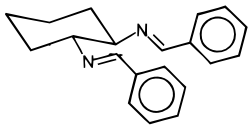
**10a** **10b** **10c**

Cy = cyclohexyl

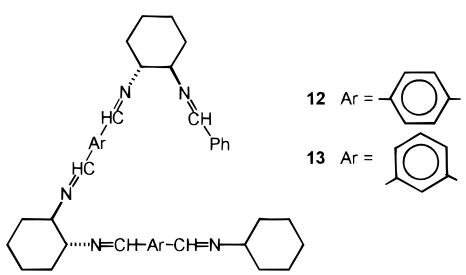
| | ΔSE (kcal/mol) |
|---|---|
| **9a** *(syn, s-trans)* | 0 |
| **9b** *(syn, s-cis)* | 0.07 |
| **10a** *(syn, s-cis$_1$)* | 0.37 |
| **10b** *(syn, s-trans)* | 0 |
| **10c** *(syn, s-cis$_2$)* | 0.58 |

in further considerations. Of all possible s-trans and s-cis arrangements of the C=N bonds in **9** and **10**, the s-trans arrangement in conformers **9a** and **10b** is favored, although SE differences are low in the case of **9** and moderate in the case of **10**. Thus, on the basis of these data, **9a** and **10b** are chosen as the candidates for the structural units of the final structures **4** and **5**, respectively.

Steric energy differences of the conformers of model structural unit of *N*,*N*′-dibenzylidene-(1*R*,2*R*)-1,2-diaminocyclohexane (**11**) were also calculated. Syn conformers were again of lower energy, the one with both the *ω* angles negative (−18°) apparently being at global energy minimum.



**11**



**12** Ar =

**13** Ar =

We next performed a molecular modeling study of the open-chain compounds **12** and **13**. These model compounds are formally obtained by overlying the phenyl rings of the components **8** + **11** + **11**, in either 1,4 or 1,3 benzene substitution pattern. The structures of **12** and **13** differ from these of the cyclic products **4** and **5** by the absence of just one imine bond, necessary to close the macrocycle. We reasoned that the calculation of steric energy of all the conformers of **12** and **13** differing in syn/anti and s-trans/s-cis conformation of the individual structural fragments, as defined in Schemes 1 and 2, will provide evidence for the existence of conformational bias for the selective formation of macrocycles **4** and **5**. Indeed, MMX steric energy minimization led to all-syn, all-trans conformational isomer of **12** (Figure 1), as the one of the lowest energy. This conformer is followed (ΔSE 0.1 kcal·mol$^{-1}$) by the one having all-syn and just one s-cis (Cy-N=CH−$C_6H_4$−CH=N−) structural feature.

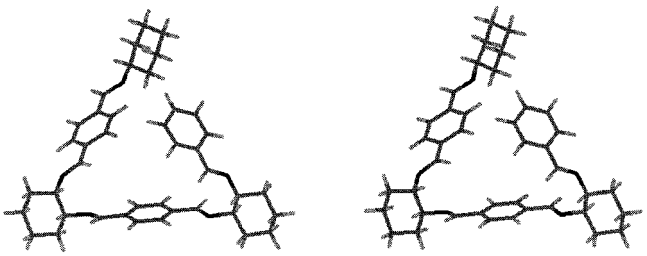


**Figure 1.** Stereoplot of the MMX force field minimized structure of **12**.

From inspection of Figure 1, it is evident that the bent structure **12** lends support for a conformational bias in the formation of the triangular macrocycle **4**. The preorganized acyclic structure analogous to **12** would allow ready cyclization to form the 30-membered macrocycle **4**, without significant loss of the internal entropy of the system.[22] Unfortunately, due to the lower symmetry of 1,3-disubstituted benzene rings in **13** this molecule did not lend itself to such a conformational analysis, which would result in a reliable low energy conformer analogous to **12**.

Steric energy minimized structures of **4** and **5**, shown in Figure 2, bear the features of their structural components, i.e., all-syn, all-trans arrangement of the imine bonds. The structures are $D_3$ and $C_3$ symmetrical, correspondingly, within the constraints of the energy minimization procedure. The calculated *ω* angles are alternating in sign, having values of −5° and 2° for **4** and −13° and 5° for **5**.

These structures are fully compatible with the recorded CD and NMR spectra. The CD spectra (Figure 3) show exciton-type Cotton effects, marked in the diagrams, with large negative amplitudes (**4**, $A = -242$; **5**, $A = -388$). These Cotton effects correspond to the allowed transitions of the diimine chromophores, at 272 nm for **4** and at 234 nm for **5**, and their negative signs are predicted for the $D_3$ or $C_3$ symmetry triple chromophoric structures having negative helicity, as determined by the absolute *R*,*R* configuration of the substituted diaminocyclohexane skeleton and the all-syn conformation of the imine

(21) For comparison, from the two reported X-ray crystal analyses of bis-salicylidene derivatives of *trans*-1,2-diaminocyclohexane we calculated the *ω* (H−C−N=C) angles respectively as 4.7°, −8.8°, and 5.8°, −3.7°. See: (a) Cannadine, J. C.; Corden, J. P.; Errington, W.; Moore, P.; Wallbridge, M. G. H. *Acta Crystallogr.* **1996**, *C52*, 1014−1017. (b) Liu, Q.; Ding, M.; Lin, Y.; Xing, Y. *Acta Crystallogr.* **1997**, *C53*, 1971−1673.

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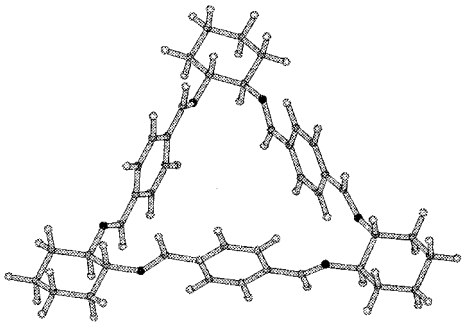
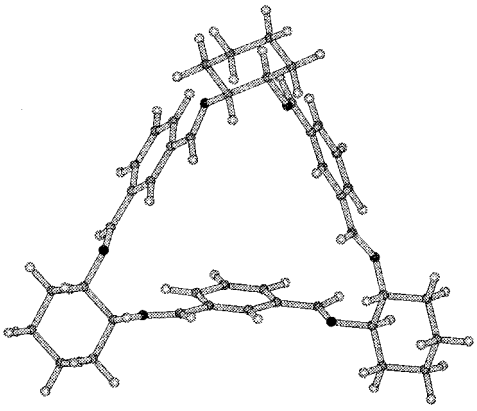


**4**



**5**

**Figure 2.** MMX force field minimized structures of **4** and **5**. Note that these structures are all-syn, all-trans, as defined in Schemes 1 and 2.

groups. Note that the exciton Cotton effect of **4** is significantly red shifted (ca. 35 nm) compared to that of **5**, as a result of more extented $\pi$-conjugation of the 1,4-phenylenediimine chromophore. In fact, the position of the Cotton effect of **5** bears close resemblance to that of the model compound **11**, whose chromophores are just the benzylidene imine units (Figure 4).

As mentioned earlier, the $^1$H NMR spectra of **4** and **5** are simple, in accordance with high-symmetry structures. The phenylene protons of **4** invariably produce a sharp singlet, in the temperature range −40° to +40 °C. The positions of the signals of aromatic protons are apparently averaged out by rapid exchange due to the low barrier of rotation of the 1,4-disubstituted benzene rings. The case of **5** is more complex, however. The aromatic region portion of the $^1$H NMR spectrum (Figure 5) at +20 °C consists of one singlet ($H_a$), one triplet ($H_c$), and a broad signal of the two protons $H_b$ which are nonisochronous due to the different conformations of the two imine substituents. This broad signal forms a pair of sharp doublets at −60 °C. This is a strong support for the s-trans conformation **10b** of the *m*-phenylenediimine structural fragment in **5**, lacking the symmetry otherwise expected for the two s-cis conformers **10a**, **10c** (see Scheme 2). The exchange of the $H_b$ and $H_{b'}$ protons is slow at ambient temperature, as it would require coordinated bond rotations around the macrocycle **5**. In addition, there are difference NOEs observed on irradiation of the azomethine proton signal of **5** at $\delta$ = 8.2, resulting in an increase of intensity of the resonance

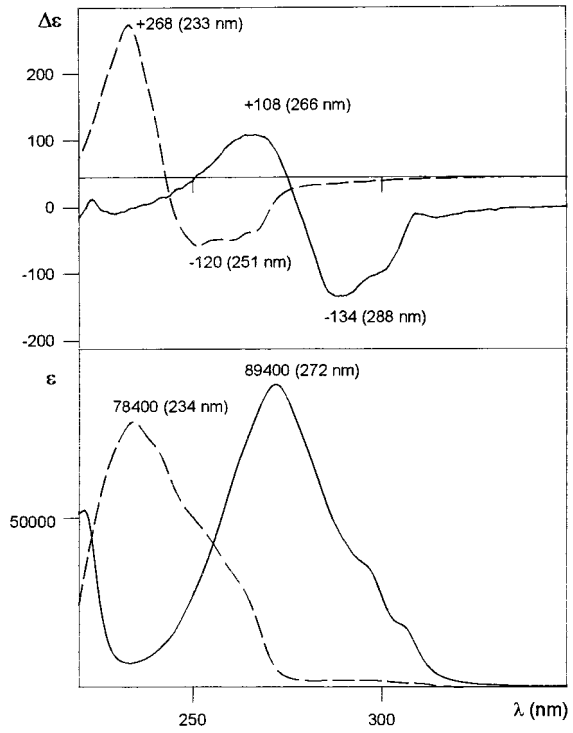



**Figure 3.** CD (top panel) and UV (bottom panel) spectra of **4** (—) and **5** (− − −), in dioxane solution.

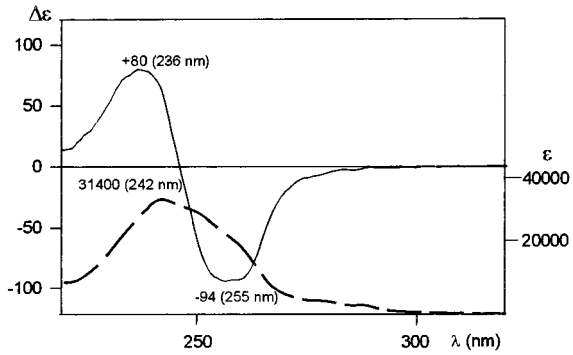



**Figure 4.** CD (—) and UV (− − −) spectra of **11**, in dioxane solution.

signals due to $H_a$ and $H_{b'}$ (7−8%), as well as due to the CH(N) protons (14%).

**X-ray Crystal Structure Determination of 4·AcOEt.** The (formally) $D_3$-symmetric molecule of **4** assumes a general position in the structure of the monoclinic crystal, and consequently all its atoms are symmetry-independent. Indeed, significant differences between chemically equivalent fragments of the macrocycle can be noted, however the structure remains all-syn, all-trans, as shown in Figure 6 and in the data of Table 1.

The torsion angles in Table 1 have been arranged into three groups corresponding to the 1,2-diaminocyclohexane-1,4-benzenediimine fragments. The largest differences between the corresponding torsion angles, of nearly 20°, exist for the N(1)−C(1) and N(2)−C(2) bonds, thus demonstrating flexibility of conformation of the imine bonds, and the next largest are for the C(7)−C(8) bonds. These differences are also reflected in the inclination of the phenyl rings. For the ideally $D_3$-symmetric macrocycle the 3-fold axis would be perpendicular to the

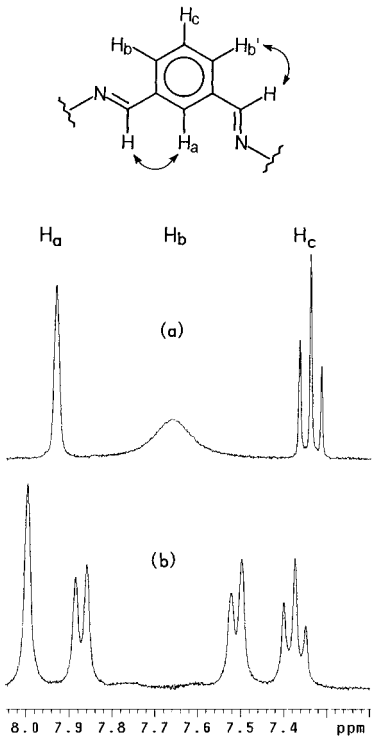



**Figure 5.** $^1$H NMR (aromatic region) spectra of **5** at +20 °C (a) and at −60 °C (b), taken in $CD_3OD$ solution.

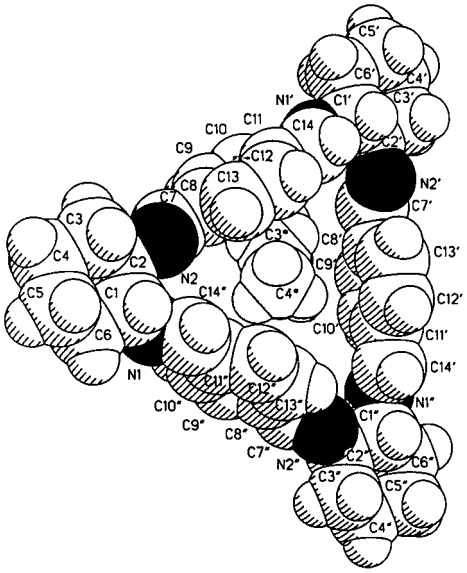



**Figure 6.** Space-filling drawing of molecule **4** (shaded, N atoms black) and of the guest ethyl acetate (unshaded), from X-ray structure determination.

macrocycle plane, and each of three 2-fold axes would pass through the midpoints of the C(1)−C(2) and C(4)−C(5) bonds of the cyclohexane rings and through the center of the phenyl rings. This symmetry would require that the phenyl rings were perpendicular to the cyclamer plane. For our calculations the molecular plane has been defined by atoms N(1), N(1′), and N(1″), and the phenyl rings are at 88.10(16), 71.0(2), and 79.38(15)° to this plane, respectively, thus they considerably depart from the $D_3$ symmetry. In this respect, the molecule of **4** is more close to symmetry $C_2$ than to $D_3$, with the pseudo-$C_2$ axis passing through phenyl C(8→13) and cyclohexane C(1"→6") rings. The departure from the $D_3$ symmetry may be due to intermolecular interactions in the crystal lattice, as each of the fragments has a different environment in the monoclinic structure—the effect enhanced by the formation of molecular complex of **4** with the low-symmetry AcOEt molecule. The guest molecule only partly penetrates the macrocyclic cavity and assumes a clearly asymmetric position relative to the macrocycle. The $D_3$-symmetric model of the isolated molecule of **4** obtained by molecular mechanics, as well as from the NMR results, indicates that the symmetry lowering of the macrocycle in the crystalline state is not induced by intramolecular strain.

**Table 1. Selected Torsion Angles (deg) in 4·AcOEt[a,b]**

| moiety | () | (′) | (″) |
|---|---|---|---|
| N(1)−C(1)−C(2)−N(2) | −63.8(8) | −64.9(8) | −66.6(8) |
| C(1)−C(2)−N(2)−C(7) | 119.6(7) | 138.9(7) | 125.6(7) |
| C(2)−N(2)−C(7)−C(8) | 180.0(6) | −175.4(7) | 176.3(6) |
| N(2)−C(7)−C(8)−C(9) | −173.9(7) | −177.2(7) | −164.8(7) |
| C(7)−C(8)−C(9)−C(10) | 179.9(7) | −174.7(7) | 176.4(7) |
| C(9)−C(10)−C(11)−C(14) | 178.9(7) | 177.5(7) | −178.6(7) |
| C(10)−C(11)−C(14)−N(1′) | −2.3(11) | −1.7(12) | 3.5(12) |
| C(11)−C(14)−N(1′)−C(1′) | −179.4(6) | −178.0(6) | −177.5(6) |
| C(14)−N(1′)−C(1′)−C(2′) | 126.2(7) | 108.7(7) | 106.8(7) |

[a] For closing up the macrocycle follow the angles from top to bottom in columns from left to right (cf. Figure 6). [b] The atomic labels as listed on the left side of the table refer to the first moiety and the first column of the angles; on moving right to the next column the labels should be primed, and for the third column when three primes appear they should be reduced to none.

## Conclusion

This work demonstrates that macrocyclic triangular structures **4** and **5** can be readily assembled from simple components **1** and **2** or **3** by conformationally driven [3 + 3] cyclocondensations. Unlike more conventional macrocycle syntheses, either template controlled or under high dilution conditions, the present method utilizes limited conformational freedom of the imine bonds formed in the condensation of the chiral diamine **1** with either of the aromatic dialdehydes **2** and **3**, combined with the directional action of the diequatorial C−N bonds in **1**. Under such conformational bias macrocycles **4** or **5** are formed selectively, rather than linear oligomeric products, as expected for the system obeying modified Curtin−Hammet principle, i.e., the major product originating from the more stable conformer.

Work on further applications of the above synthetic concept as well as on the use of the macrocycles derived is in progress.

## Experimental Section

**General Procedures.** Melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz, respectively. IR spectra were measured in KBr pellets. CD and UV spectra were taken with a JASCO 810 spectropolarimeter. FAB MS were obtained using *m*-nitrobenzyl alcohol as the matrix. Silicage plates (Merck $F_{254}$) and silica gel 60 (Merck, 230−400 mesh) were used for TLC and flash chromatographies, respectively, with dichloromethane−ethyl acetate mixtures as eluents.

**Molecular modeling** was carried out with the PC MODEL version 7.0 (Serena Software, Bloomington, IN), using the MMX force field. No influence of solvent was taken into account in these calculations.

**X-ray Crystallographic Analysis of 4·AcOEt Inclusion Compound ($C_{14}H_{16}N_2)_3$·$C_4H_8O_2$.** Crystal data and intensities were measured from a sample of 0.20 × 0.31 × 0.42 mm on a

KUMA-4 diffractometer equipped with a graphite monochromator $\lambda$(Cu K$\alpha$) = 1.541 78 Å; $\theta-2\theta$ mode used for the data collection to $\theta_{max} = 60°$; two standards monitored every 100 current reflections indicated a graduate decay of the sample crystal due to the release of guest ethyl acetate of this inclusion compound; the applied decay correction amounted to over 35% for the latest-measured intensities. The initially perfectly transparent prism turned opaque, but it did not change its orientation. Lp corrections were also applied. The structure was solved by direct methods and refined by full-matrix least squares[23] based on $F^2$'s; the H atoms were placed in optimized positions ($d_{C-H} = 0.96$ Å after each cycle of refinement with their $U_{iso}$'s increased by 1.3 compared to $U_{eq}$ of their carriers. The crystals are monoclinic, space group $P2_1$, $a = 11.569(2)$ Å, $b = 10.367(2)$ Å, $c = 18.608(4)$ Å, $\beta = 104.38(3)°$, $V = 2161.8(7)$ Å$^3$, $Z = 2$, $D_{calc} = 1.114$ g cm$^{-3}$; the final figures of merit $R1 = 0.050$ and wR2 = 0.083 for 3232 reflections and 490 refined parameters. Crystallographic data for **4·AcOEt** have been deposited with the Cambridge Crystallographic Data Centre (CCDS) as supplementary publication no. CCDC 143138. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, U.K. Fax: +44-1223-336-033. E-mail: deposit@ccdc.cam.ac.uk.

**Macrocyclic Hexaimines 4 and 5. Typical Procedure.** To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**1**) (1.14 g, 10 mmol) in dichloromethane (10 mL) was added at 0 °C a solution of either terephthaldehyde (**2**) or isophthalaldehyde (**3**) (1.34 g, 10 mmol) in dichloromethane (15 mL). The mixture was stirred at room temperature for 2−3 h, the solvent evaporated and the crude product crystallized from benzene−hexane or from ethyl acetate. Macrocycles **4** and **5** crystallized in several crops with a total yield of ca. 1.9 g, (ca. 90%). Note that **4** crystallized from ethyl acetate as a 1:1 complex.

**Compound 4:** mp does not melt up to 360 °C; $[\alpha]^{20}_D$ −356 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.48 (m, 2H), 1.80 (m, 6H), 3.37 (m, 2H), 7.52 (s, 4H), 8.14 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 24.3 ($CH_2$), 32.6 ($CH_2$), 74.4 (CHN), 128.1 ($CH_{ar}$), 137.9 ($C_{ar}$), 160.3 (CH=N); IR $\nu$ 1642 cm$^{-1}$; HREIMS *m*/*z* 636.3947, calcd for $C_{42}H_{48}N_6$ 636.3940.

**Compound 5:** mp 250−260, 276−283 °C; $[\alpha]^{20}_D$ −177 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.50 (m, 2H), 1.76 (m, 4H), 1.85 (m, 2H), 3.42 (m, 2H), 7.28 (t, $J = 7.7$ Hz, 1H), 7.60 (broad s, 2H), 7.95 (s, 1H), 8.20 (s, 2H); $^{13}$C NMR ($CD_3OD$) ä 25.5 ($CH_2$), 33.9 ($CH_2$), 75.7 (CHN), 128.9 ($CH_{ar}$), 130.2 ($CH_{ar}$), 131.9 (broad, $CH_{ar}$), 137.6 ($C_{ar}$), 163.2 (CH=N); IR $\nu$ 1647 cm$^{-1}$; HREIMS *m*/*z* 636.3914, calcd for $C_{42}H_{48}N_6$ 636.3940.

**Macrocyclic Hexaamines 6 and 7.** To a stirred solution of **4** (0.127 g, 0.2 mmol) in tetrahydrofuran−methanol (1:1, 3 mL) gradually was added solid $NaBH_4$ (50 mg), and the solution was stirred for 2 h at room temperature. After removal of solvents the residue was extracted with $CH_2Cl_2$ and water, the organic extracts were dried over $MgSO_4$, and the residue after evaporation of the solvents was crystallized from benzene−hexane, yield 0.093 g (72%).

**Compound 6:** mp 153−155° (after prolonged drying in vacuo to remove benzene); $[\alpha]^{20}_D$ −81 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.06 (m, 2H), 1.24 (m, 2H), 1.74 (m, 2H), 1.90 (broad, 2H), 2.25 (m, 4H), 3.62 (d, $J = 13.1$, 2H), 3.92 (d, $J = 13.1$, 2H), 7.30 (s, 4H); IR $\nu$ 3288, 3237 cm$^{-1}$; HRFABMS (NBA matrix) *m*/*z* 649.4911 $(M + H)^+$ calcd for $C_{42}H_{61}N_6$, 649.4958.

**Compound 7:** for $NaBH_4$ reduction of **5** methanol was used as solvent, yield 88%, oil; $[\alpha]^{20}_D$ −63 (c 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (m, 2H); 1.19 (m, 2H), 1.68 (m, 2H), 1.86 (broad s, 2H), 2.05 (m, 2H), 2.19 (m, 2H), 3.61 (d, $J = 13.2$ Hz, 2H), 3.83 (d, $J = 13.2$ Hz, 2H), 7.15−7.25 (m, 3H), 7.33 (s, 1H); IR $\nu$ 3296 cm$^{-1}$; HREIMS *m*/*z* 648.4854, calcd for $C_{42}H_{60}N_6$ 648.4879.

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