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Structural constraints for the formation of macrocyclic rhombimines

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Dedicated to Professor Marek Chmielewski on the occasion of his 65th birthday

Abstract—Rhombimines, macrocyclic tetraimines, have been obtained by the condensation of enantiomerically pure *trans*-1,2-diaminocyclohexane with aromatic dialdehydes connected by a one-atom bridge. The efficiency of the cyclocondensation is dependent upon the nature of the dialdehyde bridge atom: low selectivity was observed and rationalized by computational analysis for sp^2 hybridized bridge atoms. Unusual triple-split exciton Cotton effects were measured and calculated for highly symmetrical, tetrachromophoric rhombimines.

1. Introduction

The synthesis of chiral imine macrocycles has recently been the subject of numerous studies,[1] motivated by their potential applications as ligands and organocatalysts in asymmetric synthesis.[2] Thermodynamically controlled macrocycle formation is favored over linear oligomerization if the reactants (diamine and dialdehyde) are structurally predisposed for such a reaction, that is, there are no steric constraints for the formation of a macrocycle. It has recently been demonstrated by us, and others,[3] that enantiomerically pure *trans*-1,2-diaminocyclohexane and aromatic 1,4-dialdehydes effectively produce triangular macrocycles (trianglimines[4]) via [3+3] cyclocondensation. In addition to a variety of triangular macrocyclic oligoimines,[5–8] imine macrocycles of different shapes were obtained from *trans*-1,2-diaminocyclohexane and suitable dialdehydes. These include calixsalens,[9] loop,[10] and cigar-shaped[11] macrocyclic oligoimines. All of these macrocycles were obtained with the use of aromatic dialdehydes, such as derivatives of benzaldehyde or salicylaldehyde. Very recently, we have demonstrated that all aliphatic cyclic oligoimines derived from *trans*-1,2-diaminocyclohexane are stable molecules, unlike the highly reactive and difficult to isolate acyclic aliphatic monoimines.[11]

2. Results and discussion

Apart from trianglimines, rhombimines **3** are anticipated to be readily formed from *trans*-1,2-diaminocyclohexane **1** and suitable dialdehydes **2** of bent, but conformationally restricted, structure (Scheme 1). Indeed, plane-projected angles α and β in **3** are close to 60° and 120°, respectively, and this should provide a thermodynamic bias for the formation of [2+2] cyclocondensation products of rhomb shape, with the sum of plane–projected angles α and β equal to 360°.[12] In our preliminary communication, we have shown that when X = O, rhombimine **3a** was formed as the main product of cyclocondensation.[13] However, valence angle β in biaryls connected by a one-atom bridge X **4** is known to vary significantly (in the range 100–120°, see Table 1). This could affect the selectivity of the formation of rhombimine macrocycles. We therefore made an attempt to synthesize macrocycles **3b**–**3f** with carbon, sulfur, silicon, or nitrogen bridges between the phenyl groups.

The requisite dialdehydes **2** were prepared according to the published procedures.[14] Condensation of **1** with dialdehydes **2** (in dichloromethane at room temperature) yielded the products from which rhombimines **3** could be isolated by crystallization, except for **3f**. In this case, according to ^{1}H NMR and FAB MS analysis, a mixture was obtained, containing only minor amounts of [2+2] and [3+3] cyclocondensation products. The structures of isolated rhombimines **3b**–**3e** were confirmed by spectral analysis (^{1}H and

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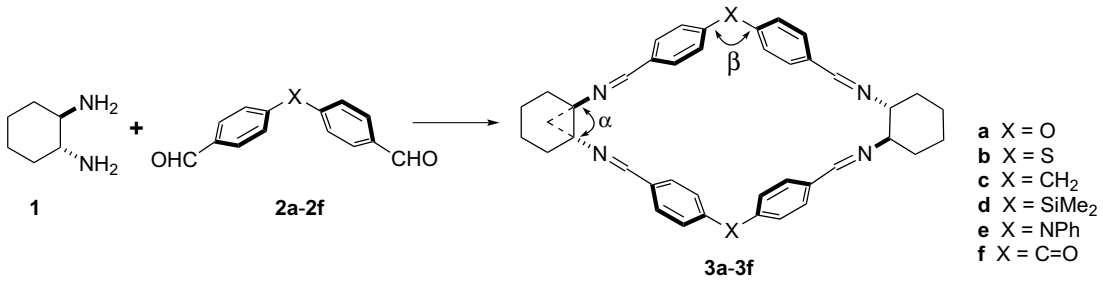


Scheme 1. Synthesis of rhombimines **3**.

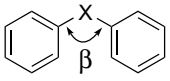
Table 1. Dihedral angles characterizing structures of oligoimine macrocycles **3a**–**3f** and model compounds **4a**–**4f**[12]

Compound	Angle (°)			
	C_{ar}–X–C_{ar}	C_{ar}=C_{ar}–X–C_{ar}	H–C–N=C	N=C–C_{ar}=C_{ar}
3a	118.2	−49.4	−16.4	−10.3
4a	120.8	40.9		
3b	103.0	−56.2	−11.8	−8.8
4b	103.9	0; 90		
3c	113.6	−70.2	−4.5	−3.4
4c	114.8	56.8		
3d	110.1	−71.3	−3.3	−2.8
4d	108.9	46.6		
3e	119.1	−46.0	−17.4	−10.3
4e	120.2	42.2		
3f	118.9	−36.1	−19.4	−17.0
4f	120.1	32.5		

Structures **3a**–**3f** are of D_2 symmetry, **4a**, **4c**–**4f** are of C_2 symmetry, **4b**—C_s symmetry.

^{13}C NMR, FAB MS, IR). Rhombimines **3d** and **3e** proved quite unstable in solution, making their purification by crystallization difficult.

We reasoned that the yields and stabilities of rhombimines **3** were affected by their structural parameters which, in the absence of X-ray data, could be obtained by computational modeling.[5] Using DFT calculations we obtained the lowest energy conformers, all of which have D_2 symmetry, with the 1,4-phenylene-X-1,4-phenylene unit in a twist conformation.[13] Structural differences between rhombimines are reflected by the magnitude of the torsion angle C_{ar}=C_{ar}–X–C_{ar}, which ranges from −36° to −71°. Table 1 presents, in addition to the valence angles C_{ar}–X–C_{ar}, also the torsion angles that characterize the structure of non-rigid parts of rhombimines **3** and model compounds **4**. Valence angle β (C_{ar}–X–C_{ar}) is the smallest for **3b** and **4b** (X = S) and it increases to ca. 120° for **3a**, **4a** (X = O), **3e**, **4e** (X = NPh) and **3f**, **4f** (X = C=O). Twist angle C_{ar}=C_{ar}–X–C_{ar} is consistently small (below 50°) for this last group of molecules (X = O, NPh, C=O), while it is generally larger for **3** compared to **4** in all cases (**a**–**f**). It should be noted that molecule **4b** is the only one having a calculated lowest-energy structure of a skew type.[13] Molecules **3a**, **3e**, and **3f** are flattened around atom X (see Fig. 1). This leads to puckering of the molecules about the imine fragments in rhombimines **3a**, **3e**, and **3f**, as evidenced by larger values of torsion angles H–C–N=C and N=C–C_{ar}=C_{ar} (Table 1).



4a-4f

a X = O
b X = S
c X = CH_2
d X = $SiMe_2$
e X = NPh
f X = C=O

Ideally, the 1,4-phenyleneimine parts of the macrocycle should be planar (N=C–C_{ar}=C_{ar} angle close to zero) and orthogonal to the mean cyclohexane ring (H–C–N=C angle close to zero). In practice, puckering makes rhombimines **3a**, **3e**, and **3f** less stable, compared to **3b**–**3d**. The differences in the shapes of rhombimines are shown in Figure 2, in which the side views of lowest energy conformers of **3c** (X = CH_2) and **3f** (X = C=O) are presented.

As an additional proof for the structural differences between rhombimines **3**, we have determined the angles within the rhombs obtained by projection of molecules **3** on the plane defined by points X and Y (see Fig. 2). For rhombimines **3b**–**3d** the angle X–Y–X is in the range from 61.5° (for **3c**), 62.8° (for **3b**) to 63.6° (for **3d**), whereas for the remaining macrocycles angle, X–Y–X is much smaller, from 52.3° (for **3f**), 53.3° (for **3a**) to 55.2° (for **3e**).[15] Since the ideal value for this angle is 60° (plane projected angle between C–N bonds in **1** and also in trianglimines), it is obvious that **3c** represents the least strained, whereas **3f** is the most strained rhombimine molecule.

Highly symmetrical (D_2) structures of rhombimines **3b**–**3e** are represented by their unique CD spectra. These molecules contain four 4-substituted phenyleneimine chromophores in a chiral arrangement. The long-wavelength transition of these chromophores is of a charge-transfer π–π^* type. There are three modes of interaction of the electric dipole transition moments of the four chromophores (Fig. 3).

The all in-phase interaction (a) results in a red-shifted transition with low intensity (formally zero) in the absorption spectrum. The other two combinations (b) contain nearly all the absorption intensity of the transition, whereas two pairs of out-of-phase interactions (c) result in a blue-shifted transition of low intensity. Exciton interaction is the main

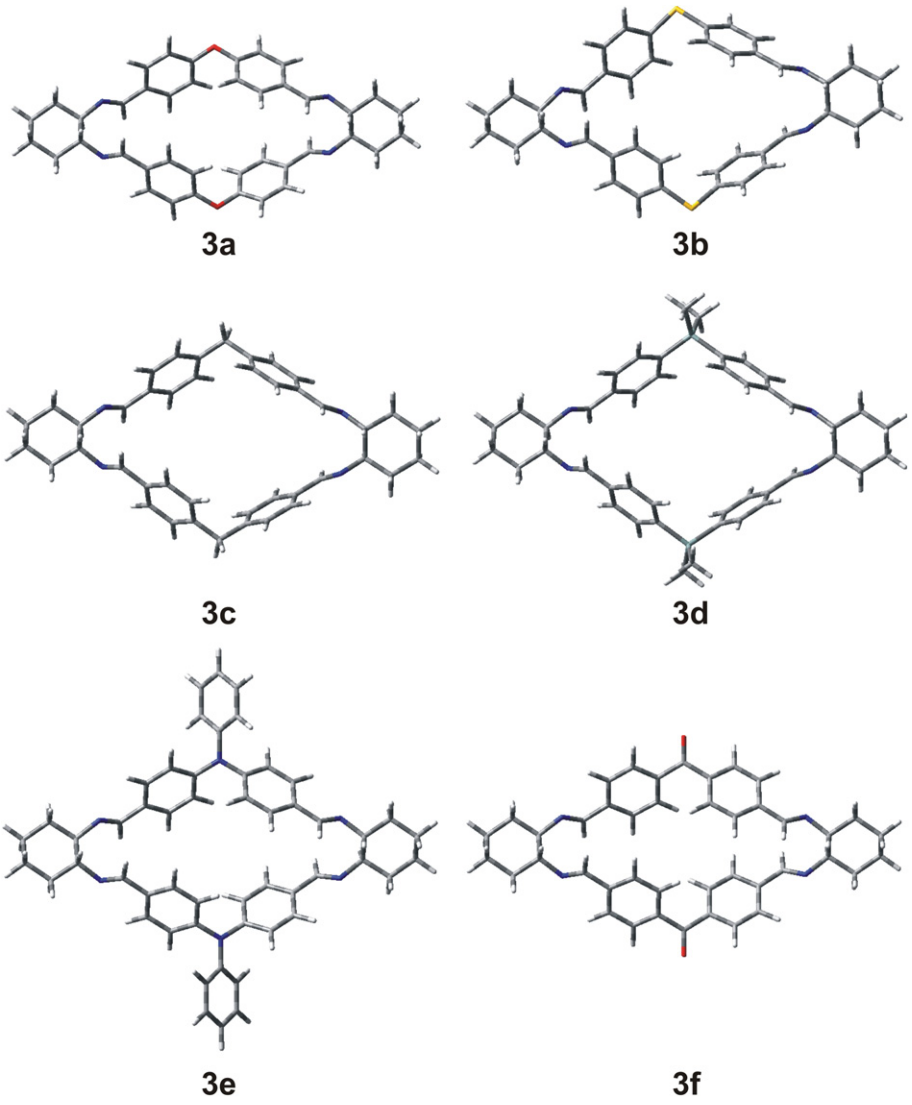


Figure 1. Structures of oligoimine macrocycles **3a**–**3f** calculated at B3LYP/6-3lG(D,P) level.

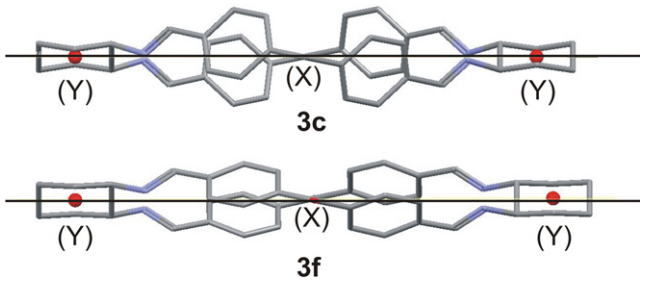


Figure 2. Side view of rhombimine molecules **3c** and **3f**, horizontal lines represent the plane marked out by atoms X and the middle points of cyclohexane rings (shown as dots Y).

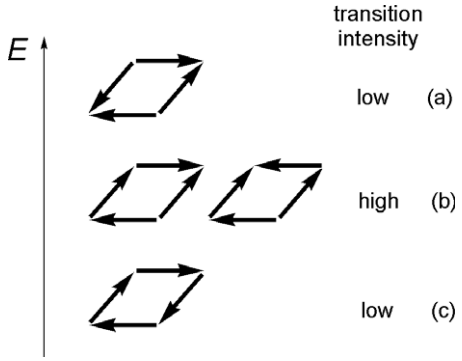


Figure 3. Modes of interaction of the electric dipole transition moments of the four 4-substituted phenyleneimine chromophores in rhombimines **3**.

contributor to the CD spectra of rhombimines **3**. As expected for the above model, three Cotton effects within the long-wavelength UV band are observed in the CD spectra of **3b**, **3c**, and **3e**, (Fig. 4), exactly as was previously seen for **3a**.[13]

The sign pattern −, +, − of the Cotton effects reflects a negative chirality of the rhombimine macrocycle due to the (*R*,*R*)-configuration of **1**. Furthermore, the experimental

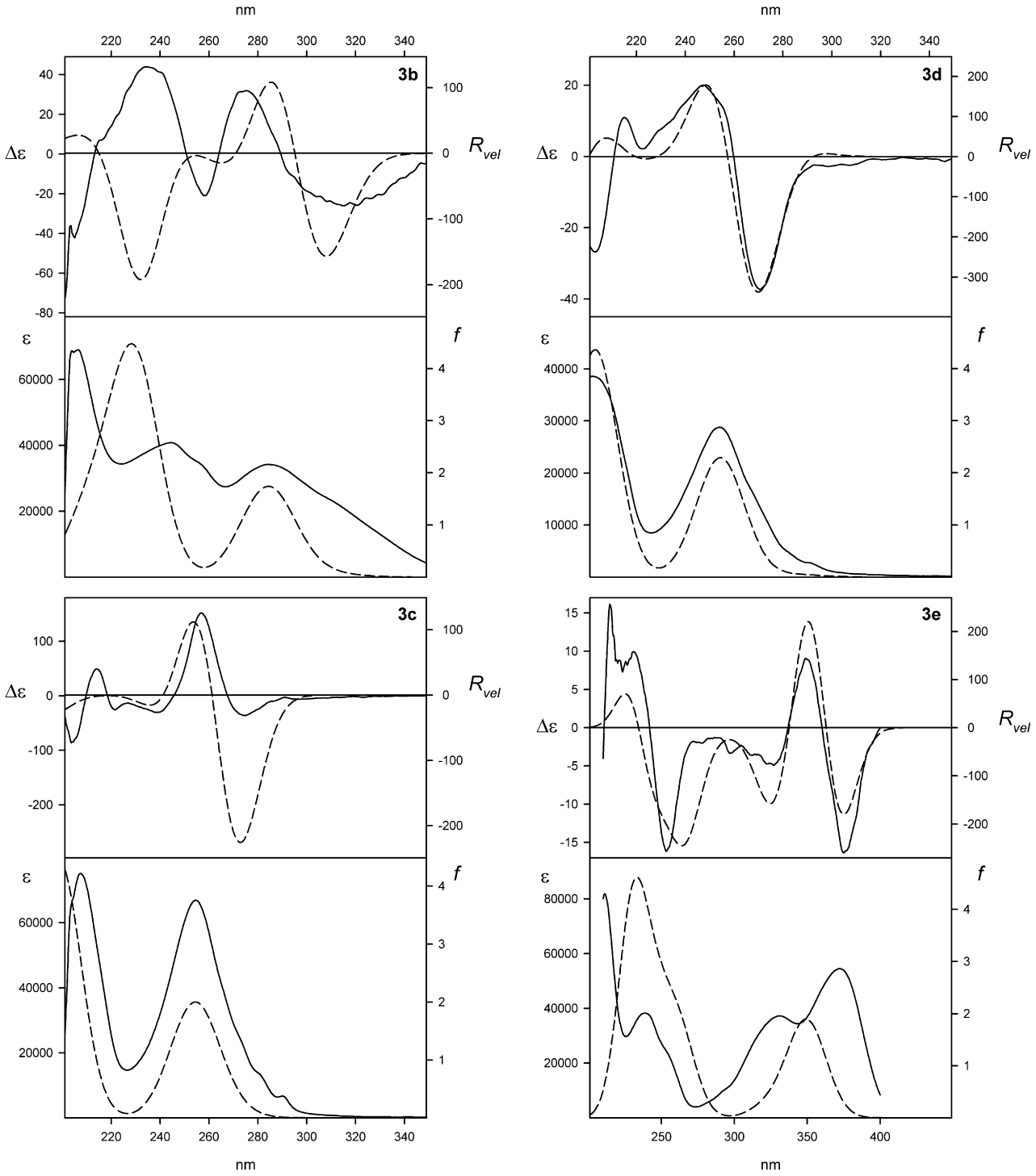


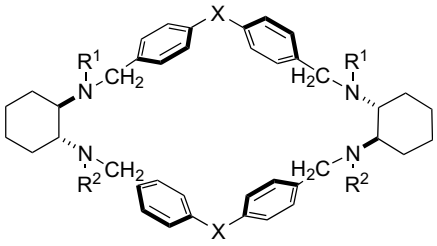
Figure 4. CD and UV spectra of oligoimines **3b**–**3e** measured in acetonitrile solution (solid line) and calculated with the use of ZINDO method (dashed line).

CD spectra of **3b**–**3e** are in full agreement with the CD spectra calculated by the ZINDO/velocity method (Fig. 4).

The CD spectrum of Si-rhombimine **3d** is exceptional. Both experimental and calculated spectra are of simple bisignate exciton type (−, +) within the long wavelength absorption band. A possible reason for this type of behavior may be a small value of the Davydov split energy for the long-wavelength allowed transition of the silicon substituted phenyleneimine chromophores.

Two of the rhombimines **3b** and **3c** were reduced by $NaBH_4$ to tetraamines (rhombamines) **5a** and **5c**, according to the previously published procedure.[5] Within the macrocycles **5a** and **5c**, two imidazolidine rings were

installed by the reaction with formaldehyde. This led to tertiary tetraamines **5b** and **5d** with a rigid structure.



5a X = CH_2, $R^1 = R^2 = H$
5b X = CH_2, R^1,$R^2 = CH_2$
5c X = S, $R^1 = R^2 = H$
5d X = S, R^1,$R^2 = CH_2$

3. Conclusion

We have shown that rhombimines **3** can be formed by simple cyclocondensation of bis-benzaldehyde molecules **2** connected by a one-atom bridge with enantiomerically pure *trans*-1,2-diaminocyclohexane **1**. This reaction is under thermodynamic control, and subtle structural differences (nature of the bridge atom) may lead to significant constraints in the macrocyclization process. Conformational analysis (DFT calculations) shows that CH_2, S, and $SiMe_2$ bridges are best suited for the formation of rhombimines. On the other hand, rhombimines with NPh and C=O bridges are significantly flattened, as the consequence of sp^2 hybridization of the bridge atom. The energy increase due to flattening of the 1,4-phenylene-bridge-1,4-phenylene portion is reduced by higher than the usually observed distortion (puckering) of the phenyleneimine part connected to a rigid *trans*-1,2-cyclohexane spacer. Consequently, the reduced stability of NPh and C=O bridged rhombimines is observed. Whereas the former is more difficult to obtain, the latter cannot be isolated from the reaction mixture. Highly symmetrical, four-chromophoric rhombimines display unique CD spectra due to exciton coupling for the long wavelength electronic transition: trisignate (−, +, −) Cotton effects were experimentally recorded and calculated by the ZINDO method.

4. Experimental

4.1. General

NMR spectra were recorded in deuteriochloroform on a Varian XL300 instrument and are reported in ppm with respect to TMS as a reference. FAB MS were measured with a 604 AMD Intectra spectrometer. FT-IR spectra were taken in KBr pellets with a Bruker IFS 113v spectrometer. CD and UV spectra were measured with a Jasco J-910 spectropolarimeter. Melting points are uncorrected.

4.2. Computational methods

The conformational search of rhombimines **3a**–**3f** was performed using PM3 hamiltonian and the lowest-energy structures were further optimized at the DFT/B3LYP/6-31G(D,P)[16] level. All the rhombimine structures corresponding to the energy minima were of D_2 symmetry. For these structures, rotational as well as oscillator strengths was calculated via the use of the ZINDO/velocity method. The CD and UV spectra were simulated by overlapping Gaussian functions for each transition. No correction for the medium dielectric constant was implemented. For rhombimines **3b** and **3d**, the calculations of CD and UV spectra at B3LYP/6-31++G(D,P) level were performed additionally. Due to their agreement with the spectra calculated by the ZINDO method, only the latter are shown and discussed. In the case of model compounds **4a**–**4f**, all calculations were performed at a B3LYP/6-311++G(D,P) level.[16]

4.3. Rhombimines 3

A solution of (1*R*,2*R*)-1,2-diaminocyclohexane (0.5 mmol), the appropriate dialdehyde (0.5 mmol), and the appropriate dialdehyde **2** (0.5 mmol) in dichloromethane (5 ml) was stirred at room temperature under argon for 24 h. The solvent was evaporated and the product crystallized or triturated with diethyl ether.

4.3.1. Rhombimine 3b. Yield (not crystallized) >90%, mp 182–183 °C; ^{1}H NMR δ 1.4–1.6 (m, 4H), 1.7–2.0 (m, 12H), 3.31 (m, 4H), 7.24 (d, $J = 8.4$ Hz, 8H), 7.41 (d, $J = 8.4$ Hz, 8H), 8.00 (s, 4H); ^{13}C NMR δ 24.5, 32.6, 73.1, 128.3, 131.2, 135.3, 137.6, 161.0; IR ν 2924, 2853, 1639, 1591, 1558, 1488, 1447, 1374, 1297, 1078, 1030, 933, 838, 815 cm^{-1}; MS *m*/*z* (relative intensity) 641 (M^++1, 49), 307 (23), 154 (100); HRMS calcd for $C_{40}H_{41}N_4S_2$ (M+1): 641.2773; found: 641.2766.

4.3.2. Rhombimine 3c. Yield 82%, mp 265 °C (from toluene–hexane); ^{1}H NMR δ 1.4–1.6 (m, 4H), 1.6–1.9 (m, 12H), 3.36 (m, 4H), 3.83 (s, 4H), 7.15 (d, $J = 8.0$ Hz, 8H), 7.44 (d, $J = 8.0$ Hz, 8H), 8.14 (s, 4H); ^{13}C NMR δ 24.6, 33.1, 42.4, 74.3, 128.3, 128.4, 134.3, 143.3,160.3; IR ν 2924, 2851, 1641, 1607, 1570, 1509, 1377, 1301, 1174, 1085, 934, 817, 808, 777, 581 cm^{-1}; MS *m*/*z* (relative intensity) 605 (M^++1, 100), 221 (21), 154 (56), 136 (44); HRMS Calcd for $C_{42}H_{45}N_4$ (M+1): 605.3644; found: 605.3663.

4.3.3. Rhombimine 3d. Yield (not crystallized) 90%, mp 168–173° C; ^{1}H NMR δ 0.07 (s, 12H), 1.4–1.6 (m, 4H), 1.8–2.0 (m, 12H), 3.39 (m, 4H), 7.45 (d, $J = 8.0$ Hz, 8H), 7.50 (d, $J = 8.0$ Hz, 8H), 8.17 (s, 4H); MS *m*/*z* (relative intensity) 693 (M^++1, 73), 265 (29), 162 (100); 1039 (3+3 cyclocondensation product, 3).

4.3.4. Rhombimine 3e. Yield 64%, mp 330–333 °C (from benzene–ethyl acetate); ^{1}H NMR δ 1.4–1.6 (m, 4H), 1.8–2.0 (m, 8H), 2.0–2.1 (m, 4H), 3.2–3.3 (m, 4H), 6.97 (d, $J = 8.5$ Hz, 6H), 7.04 (m, 6H), 7.24 (m, 4H), 7.34 (d, $J = 8.5$ Hz, 8H). 7.91 (s, 4H); ^{13}C NMR δ 23.7, 31.6, 71.5, 122.7, 123.4, 127.8, 128.3, 130.2, 145.8, 148.1, 159.2, 160.9; IR ν 2930, 2920, 2855, 1633, 1598, 1507, 1320, 1286, 1268, 1172, 838, 822, 698 cm^{-1}; MS *m*/*z* (relative intensity) 759 (M^++1, 19), 299 (18), 154 (100).

4.4. Rhombamines 5

These compounds were obtained according to the procedures reported for the related trianglamines.[5]

4.4.1. Rhombamine 5a. Yield 75%, mp 221–223 °C; ^{1}H NMR δ 1.08 (m, 4H), 1.25 (m, 4H), 1,67 (br s, 4H), 1.74 (m, 4H), 2.2–2.4 (m, 8H), 3.55 (d, $J = 3.0$ Hz, 4H), 3.90 (d, $J = 3.0$ Hz, 4H), 3.93 (s, 4H), 7.09 (d, $J = 8.1$ Hz, 8H), 7.20 (d, $J = 8.1$ Hz, 8H); ^{13}C NMR δ 25.1, 31.5, 41.2, 50.5, 61.1, 112.7, 128.0, 128.8, 139.4; HRMS calcd for $C_{42}H_{53}N_4$ (M+1): 613.4270; found: 613.4281; CD (MeOH, $\Delta\varepsilon$) +11 (230 nm), +29 (205 nm), −22 (196 nm).

4.4.2. Rhombamine 5b. Yield 87%, mp 240 °C; ^{1}H NMR δ 1.30 (m, 8H), 1.84 (m, 4H), 2.05 (m, 4H), 2.29 (m, 4H), 3.12 (d, $J = 13.4$ Hz, 4H), 3.29 (s, 4H), 3.81 (s, 4H), 4.02 (d, $J = 13.4$ Hz, 4H), 7.08 (d, $J = 8.0$ Hz, 8H), 7.15 (d, $J = 8.0$, 8H); ^{13}C NMR δ 25.0, 31.4, 49.3, 50.6, 128.4, 129.2, 130.1, 138.1; MS m/z (relative intensity) 637 (M^++1, 24), 154 (100); CD (MeOH, $\Delta\varepsilon$) −36 (230 nm), −18 (207 nm).

4.4.3. Rhombamine 5c. Yield 72%, mp 198 °C; ^{1}H NMR δ 1.2–1.3 (m, 8H), 1.6–1.8 (m, 8H), 2.2–2.4 (m, 8H), 3.61 (d, $J = 3.0$ Hz, 4H), 3.93 (d, $J = 3.0$ Hz, 4H), 7.19 (d, $J = 8.0$ Hz, 8H), 7.25 (d, $J = 8.0$ Hz, 8H); ^{13}C NMR δ 25.0, 31.0, 49.9, 60.6, 128.9, 129.1, 130.9, 138.6; MS m/z (relative intensity) 649 (M^++1, 22), 307 (23), 213 (46), 154 (100).

4.4.4. Rhombamine 5d. Yield 73%, mp 208–209 °C; ^{1}H NMR δ 1.2–1.4 (m, 8H), 1.85 (m, 4H), 2.10 (m, 4H), 2.28 (m, 4H), 3.14 (d, $J = 13.2$ Hz, 4H), 3.33 (s, 4H), 3.97 (d, $J = 13.2$ Hz, 4H), 7.17 (d, $J = 8.2$ Hz, 8H), 7.25 (d, $J = 8.2$ Hz, 8H); ^{13}C NMR δ 24.3, 29.2, 57.0, 68.5, 129.5, 131.4, 133.9, 138.4; MS m/z (relative intensity) 673 (M^++1, 52), 401 (38), 327 (55), 281 (100), 212 (81), 147 (84).

Acknowledgments

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12. Strictly speaking, macrocycles **3** are three-dimensional structures whose plane projections are polygons. However, for the purpose of simplicity of discussion and aesthetical reasons, we treat **3** as rhomboidal structures.
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15. The remaining angle Y–X–Y sums up to 180°, so it is 118.5° for **3c** and 127.7° for **3f**.
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