Rhombimines—Cyclic Tetraimines of *trans*-1,2-Diaminocyclohexane Shaped by the Diaryl Ether Structural Motif

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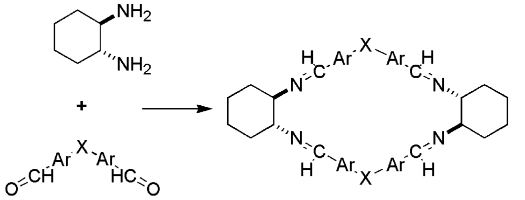

Rhombimines, chiral macrocyclic tetraimines, are preferentially formed because of the structural bias in the reaction of aromatic ether-linked dialdehydes with enantiomerically pure *trans*-1,2-diaminocyclohexane.

The selective synthesis of large-ring heterocycles (heteraphanes) is of current interest and importance, in view of their potential applications as ligands and organocatalysts (when chiral) or as scaffolds for biomimetic and nanopatterning purposes.[1] The reversible reaction of imine bond formation provides ideal conditions for building macrocyclic structures under thermodynamic control. With added conformational bias, the reaction can also be kinetically driven toward the desired, fast-forming product. Such is the case of preferential formation of chiral triangular [3+3] cyclocondensation products **4** (trianglimines) from conformationally predisposed *trans*-1,2-diaminocyclohexane (**1**) and rigid linear aromatic dialdehydes **2**[2a,b] (Scheme 1).

Large numbers of [3+3] cyclocondensation products have been obtained in recent years, frequently in high yields, from **1** and various aromatic 1,4-dialdehydes.[2c,d] With 1,3-dialdehydes, the shapes of the [3+3] cyclocondensation products are different, resembling those of calixarenes[3] (hence nicknamed calixsalens). In addition, with 1,3-dialdehydes, [2+2] cyclocondensation products **3** are often obtained in significant amounts.[4] Other diamines have also been employed for the formation of macrocyclic oligoimines.[5−7]

It can be anticipated that with the use of aromatic dialdehydes of bent structure, such as those derived from diphenyl ether, [2+2] cyclocondensation products **3**, rather than [3+3] products, will dominate. Indeed, the product of [2+2] cyclocondensation of **1** with dialdehyde **2a** has been very recently reported by Kuhnert et al.,[4b] but it had properties different from those of the one described here. Our experiments and molecular modeling study show that the preference for [2+2] cyclocondensation is general, and can be readily explained by the geometry of the macrocycle formed (Chart 1).

The cross section of macrocycles **3a** and **3b** is rhomboidal; hence the macrocycles are named rhombimines.[8] The sum of the plane-projected angles is ca. 360°; hence rhombimine molecules are considered strain-free. Whereas with rigid linear aromatic dialdehydes, trianglimines **4** having large cavities are obtained,[2d,4b] in rhombimines **3** the cavity inside the macrocycle is smaller, thus additionally stabilizing their more-compact structure.

Condensation of **1** with either aldehyde **2a** or **2b** in boiling benzene gave a mixture of imine products with high yield and a high excess of rhombimines **3** (greater than 90%), as judged by FAB MS and ^{1}H NMR data.[9] The minor products detected by FAB MS were [3+3] cyclocondensation products **4** and, in the case of dialdehyde **2a**, traces of the product of [4+4] cyclocondensation. Because the products were freely soluble, we conclude that little, if any, polymeric products were formed. Rhombimines **3a** and **3b** could be obtained as pure products (yields 68 and 42%, respectively) by simple crystallization from benzene or benzene/hexane.

The structure of diphenyl ether and its derivatives has been a subject of detailed spectroscopic and computational studies.[10,11] It has been established that the lowest-energy conformer of diphenyl ether is of twist type. Our own computational modeling (AM1 and DFT) of the structure of diphenyl ether has shown (Figure 1) that the twist conformer has the torsion angles $\omega_1 = \omega_2 = 40.9°$ (DFT b3lyp/6-311++g(d,p) structure optimization).[12] Our calculations also show that the other distinct structures

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[1] (a) Vögtle, F.; Pawlitzki, G.; Hahn, U. In *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 2. (b) Gallant, A. J.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5307. (c) Grave, C.; Schülter, A. D. *Eur. J. Org. Chem.* **2002**, 3075. (d) Akine, S.; Taniguchi, T.; Nabeshima, T. *Tetrahedron Lett.* **2001**, *42*, 8861.

[2] (a) Gawronski, J.; Kołbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768. (b) Chadim, M.; Buděšinsky, M.; Hodačova, J.; Zavada, J.; Junk, P. C. *Tetrahedron: Asymmetry* **2001**, *12*, 127. (c) Kuhnert, N.; Strassnig, C.; Lopez-Periago, A. M. *Tetrahedron: Asymmetry* **2002**, *13*, 123. (d) Kwit, M.; Skowronek, P.; Kołbon, H.; Gawronski, J. *Chirality* **2005**, *17*, S93.

[3] Kwit, M.; Gawronski, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1303.

[4] (a) Kuhnert, N.; Rossignolo, G. M.; Lopez-Periago, A. M. *Org. Biomol. Chem.* **2003**, *1*, 1157. (b) Kuhnert, N.; Burzlaff, N.; Patel, C.; Lopez-Periago, A. *Org. Biomol. Chem.* **2005**, *3*, 1911.

[5] (a) Shimakoshi, H.; Kai, T.; Aritome, I.; Hisaeda, Y. *Tetrahedron Lett.* **2002**, *43*, 8261. (b) Akine, S.; Hashimoto, D.; Saiki, T.; Nabeshima, T. *Tetrahedron Lett.* **2004**, *45*, 4225.

[6] Zhao, D.; Moore, J. S. *J. Org. Chem.* **2002**, *67*, 3548.

[7] Ma, C.; Abdolmaleki, A.; MacLachlan, M. J. *Org. Lett.* **2004**, *6*, 3841.

[8] Rhomboid coordination-driven supramolecular structure has been reported very recently: (a) Addicott, C.; Oesterling, I.; Yamamoto, T.; Müllen, K.; Stang, P. J. *J. Org. Chem.* **2005**, *70*, 797. See also related calixsalen complexes: (b) Li, Z.; Jablonski, C. *Chem. Commun.* **1999**, 1531. (c) Zhang, Y.-L.; Gao, F.; Ruan, W.-J.; Zhu, Z.-A.; Chen, Y.-T. *Chin. J. Chem.* **2001**, *19*, 1296.

[9] We note that the melting points for dialdehyde **2a** and rhombimine **3a** as well as the ^{1}H NMR data for **3a** (see the Supporting Information) are different from those reported.[4b]

[10] (a) Uno, B.; Kawakita, T.; Kano, K.; Ezumi, K.; Kubota, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2697. (b) Uno, B.; Iwamoto, T.; Okumura, N. *J. Org. Chem.* **1998**, *63*, 9794 and references therein.

[11] Verot, S.; Battesti, P. *Can. J. Chem.* **1993**, *73*, 581.

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SCHEME 1. Cyclocondensation Reaction of *trans*-1,2-Diaminocyclohexane with Various Aromatic Dialdehydes

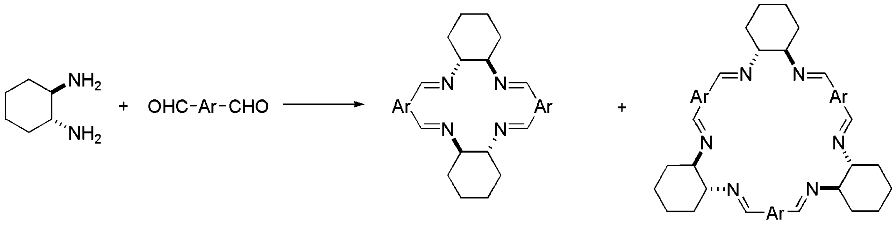
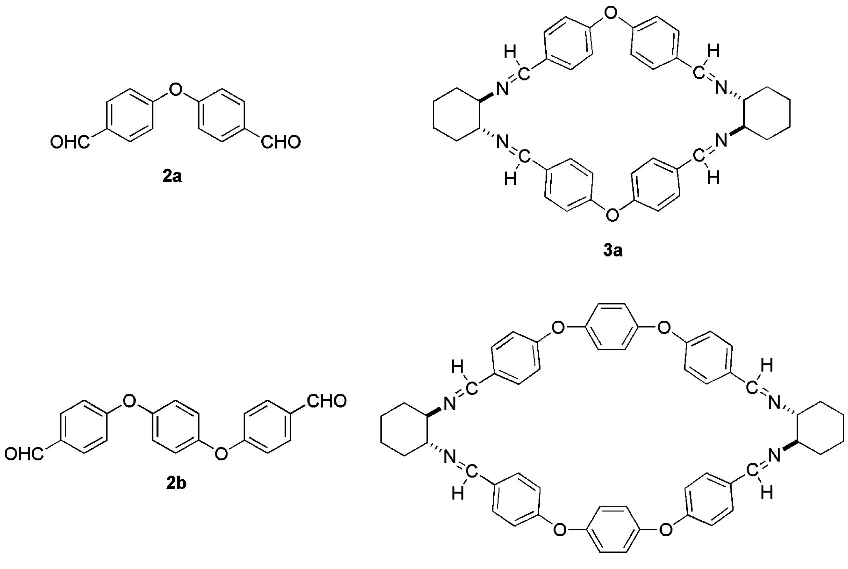


CHART 1



of diphenyl ether, i.e., the skew (*S*) and the butterfly (*B*) conformations, are not the energy minima, as previously claimed,[10] but are rather the transition states, whereas the planar form (*P*) is the second-order saddle point (see the Supporting Information).

Recently, X-ray determined structures of diphenyl ether[9] and dialdehyde **2a**[4b] show that their conformations in the crystal are skew ($\omega_1 \approx 0$, $\omega_2 \approx 90°$). It has been shown by spectral measurements and CNDO/S-CI calculations that the conformation of the diaryl ether moiety is controlled by the nature of the 4-substituent: an electron-accepting substituent (such as the formyl group) in the ring stabilizes a skew conformer, by an intramolecular charge-transfer interaction of the electron-accepting group with a lone-pair orbital of the bridging oxygen atom.[10b]

Using either the twist or skew structures of the diphenyl ether units and the structural features determined previously for macrocyclic imines,[2a] i.e., the coplanarity of the phenyl and imine groups, the *E* configuration of the imine groups as well as the *syn* conformation of the imine C−H and the adjacent cyclohexane axial C−H bonds as the input parameters, we computed the

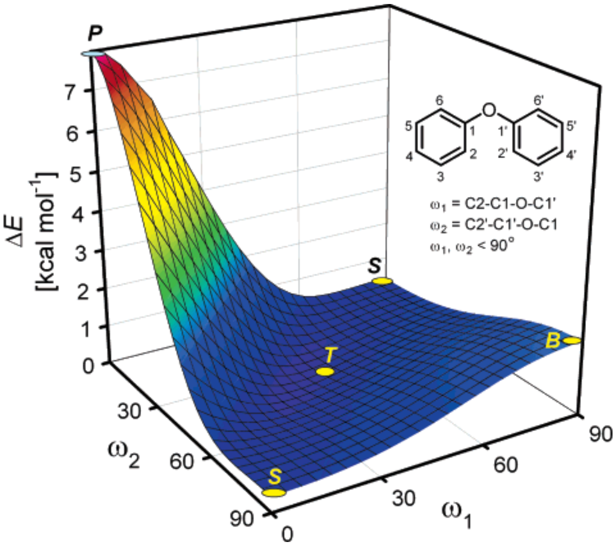


FIGURE 1. Computed energy profile (AM1) of the diphenyl ether molecule as a function of the rotation of torsion angles ω_1 and ω_2. *T* indicates the lowest-energy twist conformer, and the *S* (skew), *B* (butterfly), and *P* (planar) structures are the saddle points.

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(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2001.

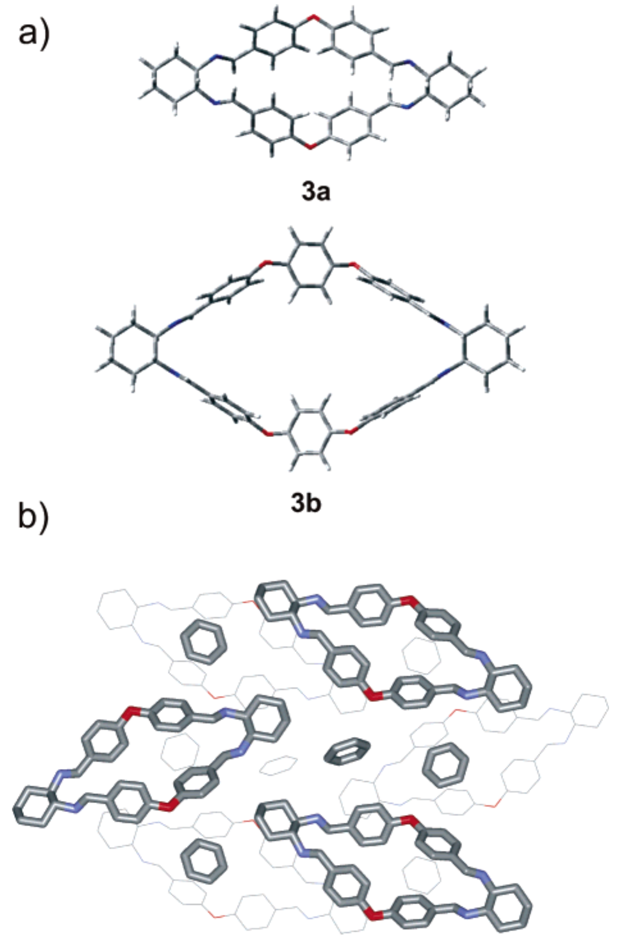


FIGURE 2. (a) Computed lowest-energy structures of rhombimines **3a** and **3b**. (b) Part of the crystal structure of **3a**, viewed down the x-axis. Two consecutive molecular layers are differentiated by thick and thin lines. The benzene guest molecules are distributed over two different sites. One half is situated in channels that run along the x-axis, i.e., roughly perpendicular to the molecular plane; the other half is situated between molecules related by translation along x.

structures of tetraimines **3a** and **3d** by the PM3 method. The only stable conformers thus obtained were the rhombimines of D_2 symmetry, shown in Figure 2. Note that in these structures the imine bonds in the same diaryl ether linkage are *anti* oriented, as found for trianglimines.[2a]

In addition, we were able to determine the structure of **3a** in the crystal by X-ray diffraction analysis. Rhombimine **3a** crystallized from benzene with two molecules of the solvent molecule; its symmetry was C_2. The computed and experimentally determined structures are quite close; in both cases the diaryl ether conformations are of twist type; the ω values are $-49°$ (computed) and $-30°$ and $-55°$ (X-ray determined). In the crystal structure, the phenyl groups are not ideally coplanar with the imine bonds; the torsion angles around the $C_{Ar}-C_{C(N)}$ bonds vary between -4.7 and $-13.8°$.

As a final test of correctness of the determination of the molecular geometry of rhombimines **3a** and **3b** in solution, we have computed (ZINDO/velocity method) the CD spectra of their lowest-energy conformers, shown in Figure 2. When confronted with the experimental CD spectra (Figure 3), we noted a very good agreement regarding the signs and relative magnitudes of the Cotton effects, attesting to the correctness of the assigned structure. It is noteworthy that in the case of rhombimine **3a**, an unusual triple-split Cotton effect with the signs sequence $-$, $+$, $-$ is observed and calculated for the allowed charge-transfer $\pi-\pi^*$ transition of the 4-oxybenzimine chromophore at ca. 263 nm. This pattern of exciton-split Cotton effects can be predicted qualitatively by taking into account the modes of interaction of the electric dipole transition moments of the four 4-oxybenzimine chromophores. The all in-phase interaction produces a red-shifted transition with minimum intensity in the absorption spectrum. The three in-phase/one out-of-phase combination follows, with nearly all of the intensity residing within this transition, whereas two pairs of out-of-phase interactions lead to a blue-shifted transition of low intensity. The corresponding negative long-wavelength Cotton effect reflects the negative chirality of the rhombimine macrocycle imposed by the (R,R)-configuration of **1**.

$NaBH_4$ reduction of rhombimines **3a** and **3b** cleanly afforded the corresponding tetraamines (rhombamines **5a** and **5b**, Chart 2; see also the Supporting Information).

In addition, we have synthesized less-symmetrical heteraphanes from **1** and 3,3′- or 3,4′-oxybisbenzaldehyde. According to molecular modeling, these [2+2] cyclocondensation products also have the structures with parallel sides (C_1 or C_2 symmetry) when plane-projected; hence they resemble the structures of rhombimines. Regrettably, they could not be purified by conventional methods, e.g., crystallization (for characterization see the Supporting Information).

In summary, the present study shows that rhomb-shaped tetraimine macrocycles **3** are preferentially formed in the reaction of *trans*-1,2-diaminocyclohexane with aromatic dialdehydes having the ether linkage. Rhombimines **3** are in this case evidently thermodynamically more stable than the corresponding [3+3] cyclocondensation products (trianglimines **4**): the plane-projected N−C/C−N bond angle in **1** (ca. 60°) is nicely matched by the aromatic ether C−O−C bond angle (ca. 120°) to provide a compact, strain-free rhomboid product. The aromatic ether moiety in all the cases investigated has a twist or close to a skew conformation. Work is now in progress on the synthesis and applications of rhombimines having an alternative to oxygen one-atom bridges between the aromatic aldehyde moieties.

Experimental Section

Cyclic Tetraimines 3a and 3b. Typical Procedure. To a stirred solution of aromatic dialdehyde **2a** or **2b** (1 mmol) in benzene (5 mL) was added a solution of (1R,2R)-1,2-diaminocyclohexane (**1**, 1 mmol) in benzene (1 mL). The solution was refluxed for 3 h with azeotropic water removal. After evaporation of the solvent, crude product was crystallized from benzene (compound **3a**, as a 1:2 complex, slowly losing the solvent) or from benzene/hexane (compound **3b**).

Compound 3a: yield 68%; mp 308−310 °C (lit.[4b] mp 120 °C dec); ^{1}H NMR ($CDCl_3$) δ 1.51 (m, 4H), 1.91 (m, 8H), 2.10 (m, 4H), 3.22 (m, 4H), 6.81 (d, J = 8.8 Hz, 8H), 7.36 (d, J = 8.5 Hz, 8H), 7.80 (s, 4H); IR ν 1642 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.5 (CH_2), 32.2 (CH_2), 72.9 (CHN), 118.7 (CH_{Ar}), 129.4 (CH_{Ar}), 131.8 (C_{Ar}), 158.7 (C_{Ar}), 162.3 (CH=N); HR FAB MS m/z 609.32189 (M + H)$^+$, calcd for $C_{40}H_{41}O_2N_4$ 609.32294.

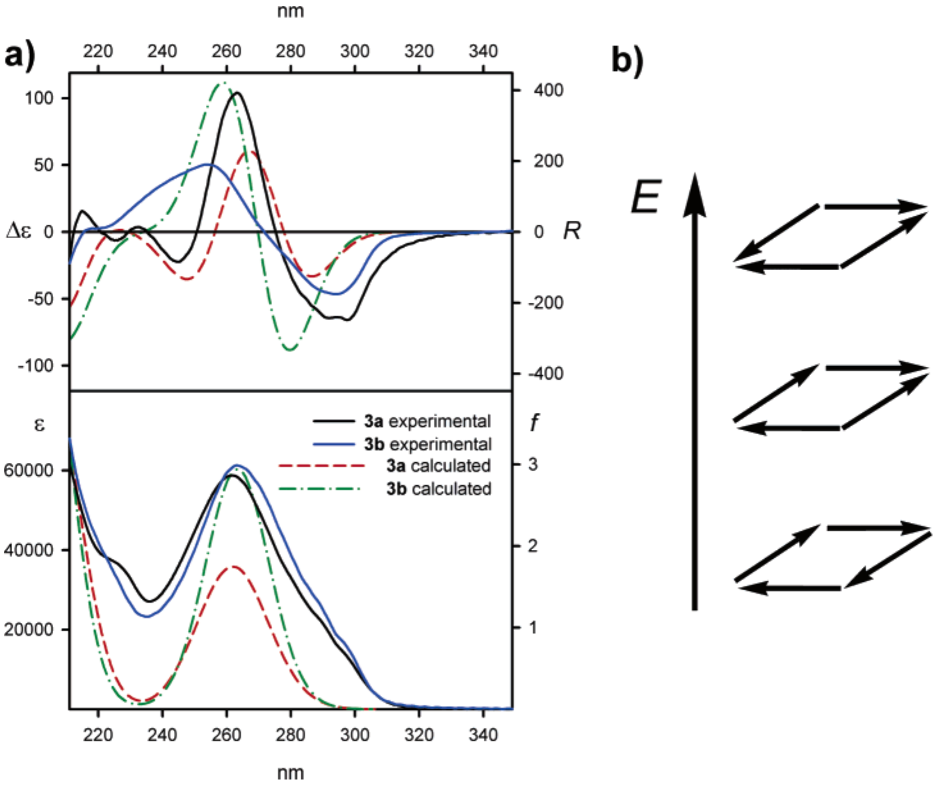
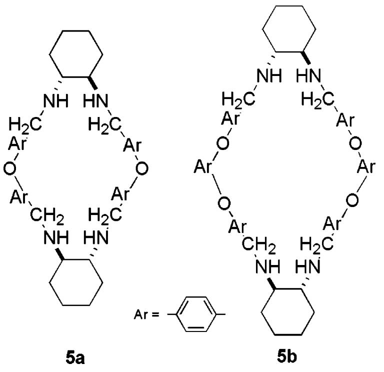


FIGURE 3. (a) Experimental (in acetonitrile solution) and computed (ZINDO method) CD (upper panel) and UV (lower panel) spectra of **3a** and **3b**. The computed transition energies were scaled by a factor of 0.92 to match the experimental UV maxima. (b) The modes of interaction of the electric dipole transition moments of the four 4-oxybenzimine chromophores in rhombimine **3a**.

CHART 2



Compound 3b: yield 42%; mp 302−304 °C; ^{1}H NMR (CDCl$_3$) δ 1.49 (m, 4H), 1.78 (m, 12H), 3.40 (m, 4H), 6.92 (d, J = 8.5 Hz, 8H), 6.96 (s, 8H), 7.58 (d, J = 8.5 Hz, 8H), 8.20 (s, 4H); ^{13}C NMR (CDCl$_3$) δ 24.5 (CH$_2$), 33.1 (CH$_2$), 74.3 (CHN), 117.7 (CH$_{\mathrm{Ar}}$), 121.1 (CH$_{\mathrm{Ar}}$), 129.5 (CH$_{\mathrm{Ar}}$), 131.4 (C$_{\mathrm{Ar}}$), 152.3 (C$_{\mathrm{Ar}}$), 159.5 (CH=N); IR ν 1643 cm^{-1}; HR FAB MS m/z 793.37617 (M + H)$^+$, calcd for $C_{52}H_{49}O_4N_4$ 793.37537.

Cyclic tetraamines **5a** and **5b** were prepared following the published procedure.[2a]

Compound 5a: yield 78%; mp 181−183 °C; ^{1}H NMR (CDCl$_3$) δ 1.10 (m, 4H), 1.28 (m, 4H), 1.79 (m, 8H), 2.28 (m, 8H), 3.54 (d, J = 12.6 Hz, 4H), 3.89 (d, J = 12.6 Hz, 4H), 6.90 (d, J = 8.5 Hz, 8H), 7.23 (d, J = 8.5 Hz, 8H); IR ν 3298 cm^{-1}; HR FAB MS m/z 617.38454 (M + H)$^+$, calcd for $C_{40}H_{49}O_2N_4$ 617.38556.

Compound 5b: yield 65%; mp 208−212 °C; ^{1}H NMR (CDCl$_3$) δ 1.23 (m, 8H), 1.97 (m, 8H), 2.25 (m, 8H), 3.57 (d, J = 12.9 Hz, 4H), 3.87 (d, J = 12.6 Hz, 4H), 6.94 (d, J = 9.3 Hz, 8H)), 6.97 (s, 8H), 7.24 (d, J = 9.3 Hz, 8H); IR ν 3291 cm^{-1}; HR FAB MS m/z 801.44045 (M + H)$^+$, calcd for $C_{52}H_{57}O_4N_4$ 801.43799.

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Supporting Information Available: Detailed experimental data for starting dialdehydes; ^{1}H and ^{13}C NMR spectra of dialdehydes and rhombimines; detailed results and computation procedures for the structures and CD/UV spectra of rhombimines; and details of the crystal structure determination of rhombimine **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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