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Chiral calixsalen-type macrocycles from *trans*-1,2-diaminocyclohexane

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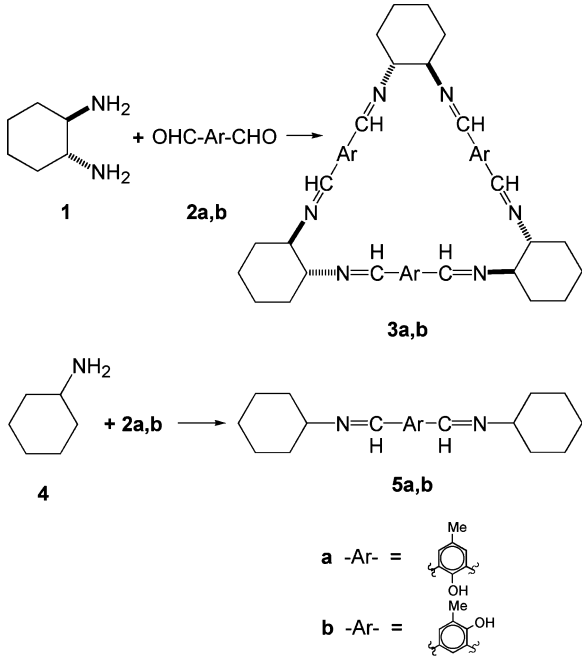
Abstract—The readily obtained products **3a** and **3b** from the [3+3] cyclocondensation of *trans*-1,2-diaminocyclohexane **1** with hydroxydialdehydes **2a** or **2b** have vase-like structures. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Calixarenes are the cyclocondensation products of phenols or resorcinols with aldehydes.[1,2] Numerous heteroanalogues as well as homologues of calixarenes exhibiting vase-like structures are known. Cyclic Schiff bases, the products of cyclocondensation of aromatic dialdehydes with diamines, may also fall into the class of vase-like molecules, called calixsalens,[3] when derived from a hydroxydialdehyde and a diamine. Recently we[4] and others[5] reported on the remarkable self-assembly of a [3+3] cyclocondensation product of *trans*-1,2-diaminocyclohexane (DACH) and terephthaldehyde to give a triangle-shaped product. Analogous reaction with isophthaldehyde produced a [3+3] cyclocondensation product whose structure, according to spectroscopic data and molecular modeling studies, was vase-like.[4] In this structure the upper rim was formed by the imine-substituted benzene rings fragments and the cyclohexane rings whereas the lower rim was made up from methyl-substituted parts of the benzene rings. Very recently Kuhnert et al. reported on DACH-based hexaimine macrocycles (trianglimines) having substituted isophthalyl, terephthalyl, biphenyl or 9,10-anthracenyl linkers, the latter two with a much larger central cavity.[6] It is of importance to note that these derivatives of DACH are chiral and may find use as ligands and resolving agents. Placement of the hydroxy group in the dialdehyde molecule may additionally stabilize the structure of the cyclic product and may serve to enhance its complex-forming behavior. In this communication we report the synthesis and structural assignment of macrocycles **3a** and **3b** from (*R*,*R*)-1,2-diaminocyclohexane **1** and two hydroxy-substituted isophthalic aldehydes, **2a** and **2b** (Scheme 1).



Scheme 1.

Compound **3a** was originally obtained by a high dilution technique, however its structure has not been investigated (the X-ray structure of its hexaamine reduction product was obtained).[7]

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2. Results and discussion

We have found that both **3a** and **3b** can be obtained in yields of 80 and 78%, respectively, by the reaction of **1** with **2a** or **2b** under ordinary reaction conditions (concentration 0.4 M in chloroform, room temperature, overnight) (Scheme 1). The reaction is apparently driven by the structural predisposition of the intermediate imine products as well as by thermodynamic stability of the macrocycles **3a** and **3b**.

The trimeric structures of **3a** and **3b** were ascertained by FAB MS analysis: the molecular ion peaks at m/z 727 correspond to the $(M+H)^+$ ions of the [3+3] cyclocondensation products. However, the stereochemical features of the macrocycles **3a** and **3b** required more systematic studies. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ shows two peaks for the imine protons at $\delta =$ 8.67 and 8.22, as well as two signals for the aromatic protons at $\delta = 7.62$ and 6.96, in agreement with the *s-trans* conformation of the bis-imine system. These signals are slightly broadened at ambient temperature, apparently due to the correlated rotation of the imine groups.[8] There is only one signal for the CH(N) protons in the cyclohexane rings, and one signal for the methyl groups, indicating that macrocycle **3a** has C_3-symmetry. According to these data and our previous analysis of the analogous trimeric cyclocondensation products[4] we assume a *syn* conformation of the imine C–H/cyclohexane axial C–H bond systems and *s-trans* conformation of the bis-imine unit (Fig. 1).

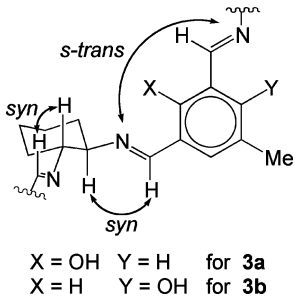


Figure 1. Partial structures of the trimeric cyclocondensation products **3a** and **3b** showing stereochemical features.

The preference for the *syn* conformation is well supported by the results of ab initio computations carried-out for the *syn* and *anti* conformers of the model compound, *N*-benzylidenecyclohexylamine (Fig. 2). In the *anti* conformer the methine hydrogen atom and each of the two vicinal axial hydrogen atoms in the cyclohexane ring are brought into close contact (2.37 Å), strongly destabilizing ($\Delta E \geq 3.5$ kcal mol^{-1}) this structure. Available X-ray diffraction data for salicylidene derivatives of DACH also support the preference for the *syn* conformation.[9]

The UV and CD spectra of **3a** are quite complex in the region of the strong absorption, 200–300 nm (Fig. 3).

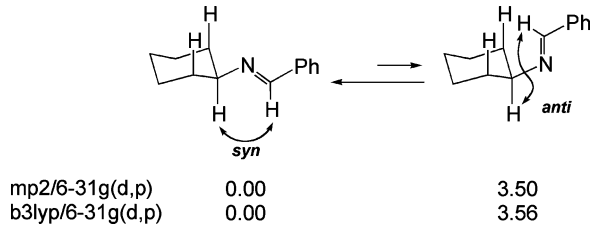


Figure 2. Computed energy differences (ΔE, kcal mol^{-1}) of the *syn* and *anti* conformers of *N*-benzylidenecyclohexylamine.

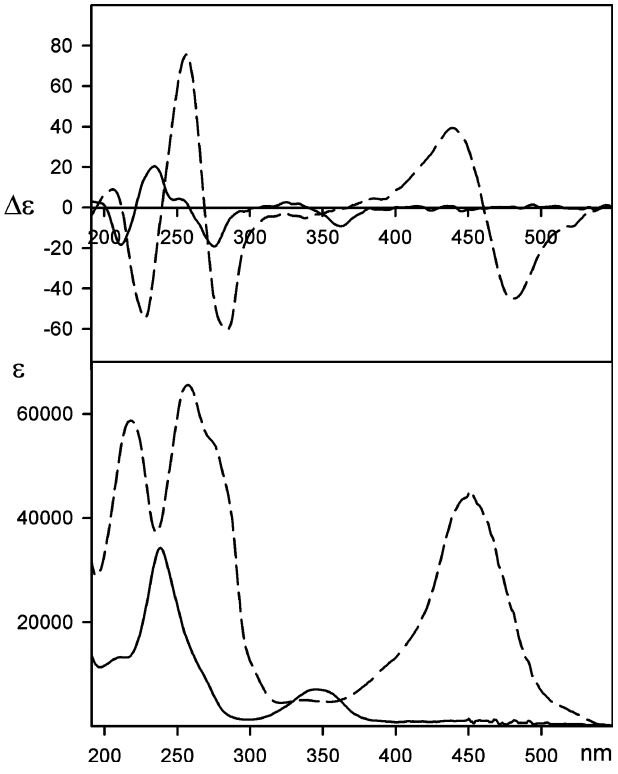


Figure 3. CD (upper panel) and UV (lower panel) of **3a** in acetonitrile (full line) and in acidified acetonitrile solution (broken line).

The weak absorption band at ca. 350 nm upon protonation is bathochromically shifted to 450 nm and significantly enhanced.

This absorption band, according to the semiempirical INDO/S-CI calculation, is associated with the excited state polarized along the N----N axis (Fig. 4). The CD spectrum of **3a** shows a negative exciton-split Cotton effect centered around 460 nm. The sign of this Cotton effect is in agreement with the conformation shown in Figure 1 (electric dipole transition moment is approximately parallel to the direction of the C–N bond attached to the cyclohexane ring). There is no change in the conformation upon protonation, according to the ^{1}H NMR data.

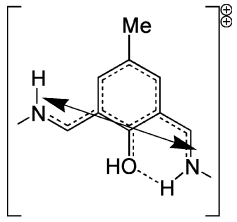


Figure 4. Direction of the electric dipole transition moment for the longest-wavelength absorption band in the protonated chromophore of **3a**.

In the case of **3b** the conformation of the macrocycle can again be inferred from the ^{1}H NMR and CD data. There are only four singlet resonance signals corresponding to the two non-equivalent aromatic protons and two non-equivalent imine protons, as well as just one methyl group signal, indicating a highly ordered C_3-symmetrical structure of the macrocycle. In order to assign these signals we performed NOE experiments, summarized in Figure 5.

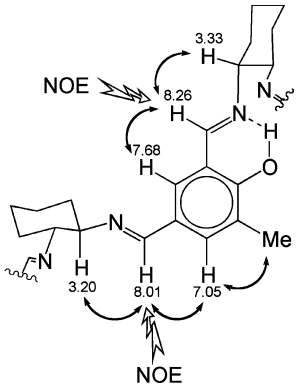


Figure 5. Assignment of the NOEs in **3b**.

Irradiation of each of the methine signals at $\delta = 8.01$ or 8.26 brought about NOEs with the vicinal proton signals, both in the cyclohexane ring and in the benzene ring. The structure shown in Figure 5 is fully compatible with the partial structure displayed in Figure 1. Moreover, the structure provides foundation for the interpretation of the CD spectrum generated by macrocycle **3b**. The most intense absorption band in the UV spectrum of **3b** is located at 242 nm (ε 82500), as shown in Figure 6. According to INDO/S-CI computation this band is due to the π–π^* transition polarized as shown in Figure 4 for **3a**, i.e. in the direction parallel to the direction of the C–N bonds in the cyclohexane skeleton. Unlike the case of macrocycle **3a**, the CD spectrum of **3b** displays a very strong negative exciton Cotton effect associated with the 242 nm band, with the amplitude −340 ($\Delta\varepsilon$ at 259 nm −157, $\Delta\varepsilon$ at 242 nm +183) while in acidified acetonitrile solution the Cotton effect around 450 nm is very weak. These negative exciton Cotton effects are fully consistent with the partial structure shown in Figure 1.

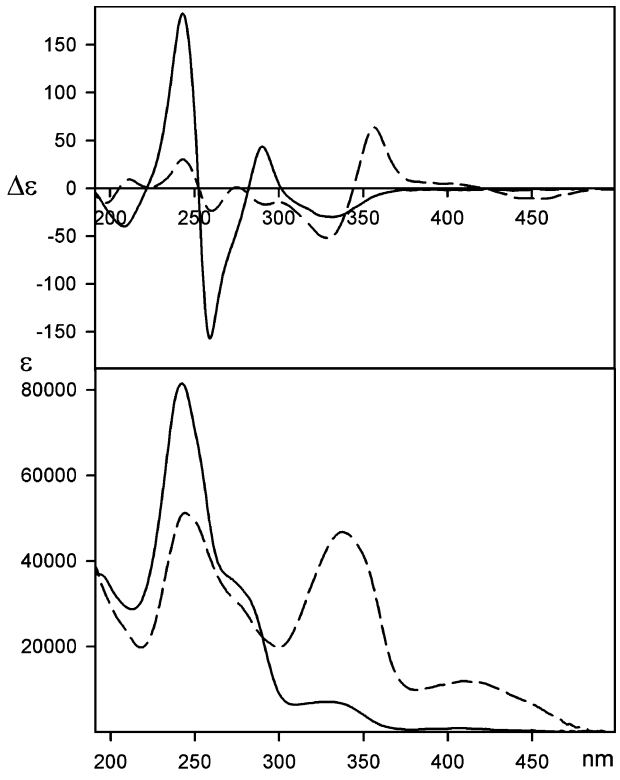


Figure 6. CD (upper panel) and UV (lower panel) of **3b** in acetonitrile (full line) and in acidified acetonitrile solution (broken line).

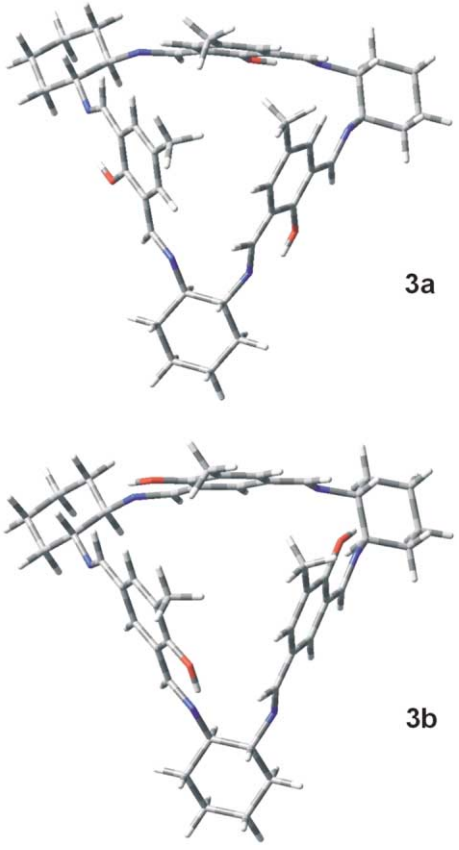


Figure 7. Computed structures of the calixsalens **3a** and **3b** shown with lower rim up.

The computed lowest-energy structures of macrocycles **3a** and **3b**, obtained by semiemprical PM3 method, are shown in Figure 7.

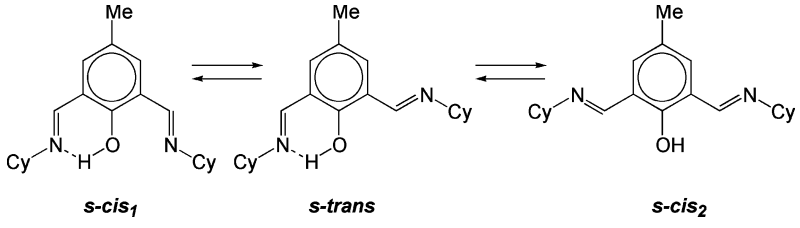
The featured structures are vase-like, with the lower rim consisting of the methyl-substituted benzene fragments and the upper rim containing the cyclohexane rings. The symmetry of these calixsalen-type macrocycles is C_3 and the specific structural features are the all-*syn* conformation of the imine bonds and the *s-trans* conformation of the diimine fragment (see Fig. 1). The specific torsion angles H–C*–N=C are pairwise −31.9 and 30.7° for **3a** and −28.0 and 28.1° for **3b**, while angles α and β are correspondingly −1.2 and 176.5° for both compounds.

We found it of interest to compare the structural features of macrocycles **3a** and **3b** with those of the corresponding monomeric Schiff bases **5a** and **5b**, derived from dialdehydes **2a** and **2b** by the condensation with 2 equiv. of cyclohexylamine **4** (Scheme 1). Schiff base **5a** can exist as a mixture of conformers, two *s-cis* and one *s-trans*, according to Scheme 2.

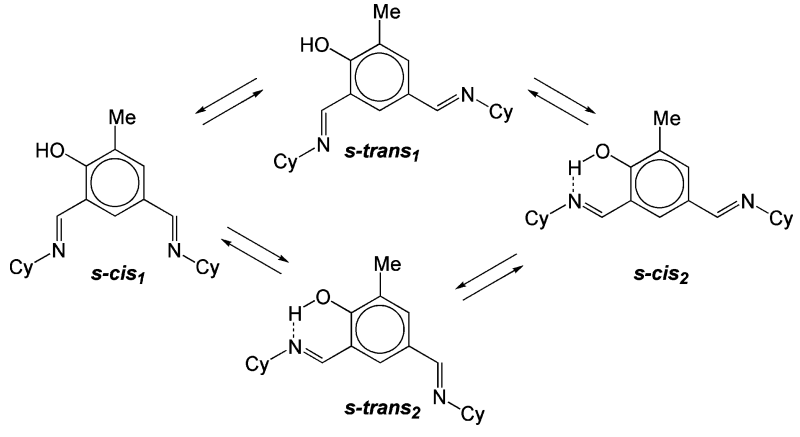
The ^{1}H NMR spectrum of **5a** at room temperature shows two broad, unresolved signals of the aromatic protons ($\delta = 6.8$–8.0), as well as broadened signal of the methine protons ($\delta = 8.6$). These signals resolve into four singlets of equal intensity ($\delta = 8.86$, 8.35, 7.80, 7.14) upon cooling the sample to 223 K. Symmetry arguments point to the *s-trans* conformer as the dominating one. From the coalescence temperature (292 K) we obtained the free enthalpy of activation 13.7 kcal mol^{-1} for the rotation of the imine C_{ar}–C(=N) bond. This relatively high barrier to rotation in $CDCl_3$ solution may be due to the stabilizing effect of the intramolecular hydrogen bond between the phenol group and the imine nitrogen which is present in the *s-trans* conformer.[8] DFT calculations at the mp2/6-31g*//b3lyp/6-31g* level indeed indicate the *s-trans* conformer of **5a** to be the most stable one, followed by the *s-cis*$_1$ conformer (ΔE 11.18 kcal mol^{-1}). Interestingly, the analogue of **5a** with phenyl groups in place of the cyclohexyl groups was found to exist in the *s-trans* conformation in the solid state, according to the results from X-ray diffraction analysis.[10] In the case of Schiff base **5b** the ^{1}H NMR spectrum in $CDCl_3$ at 293 K demonstrates the presence of two distinct species of equal population, i.e. there are two signals for the methyl groups ($\delta = 2.28$ and 2.24), four signals for the aromatic protons ($\delta = 7.46$, 7.36, 7.00, 6.84), four signals for the methine protons ($\delta = 8.34$, 8.29, 8.18, 7.60) and two broad signals for the phenol protons at $\delta =$ 14.59 and 13.97. The most stable conformers of nearly equal energy, according to DFT computation at the b3lyp/6-31++G**//b3lyp/6-31g** level, are the two with the intramolecular hydrogen bond, i.e. *s-trans*$_2$ and *s-cis*$_2$ (Scheme 3).

3. Conclusions

These results demonstrate that the acyclic bis-Schiff bases **5a** and **5b** can exist as an equilibrium mixture of intramolecularly hydrogen-bonded conformers *s-cis* and *s-trans*. In the cyclic trimeric structures **3a** and **3b**, derived from DACH geometrical constraints require



Scheme 2.



Scheme 3.

the diimine fragment to adopt the *s-trans* conformation, which is stabilized by an intramolecular hydrogen bond in the salen type derivatives. As a result, cyclic trimeric salens have vase-like structure, and hence are described as calixsalens. As with calixarenes, the hydroxy groups in calixsalen **3a** point in the direction of upper rim—a remarkable feature that should be useful in future applications.

4. Experimental

4.1. General procedures

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. IR spectra were measured in KBr pellets. CD and UV spectra were taken with a JASCO J-810 spectropolarimeter. All DFT and ab initio calculation were performed using the Gaussian-98 suite of programs.[11] Structures **3a** and **3b** were computed by the semiempirical PM3 method, and INDO/S-CI calculations were performed using CAChe WS Pro 5.[12] 2,4-Diformyl-6-methylphenol **2b**[13] and diimine **5a**[14] were obtained according to reported procedures.

4.2. Macrocyclic hexaimines 3a and 3b

To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane **1** (0.114 g, 1 mmol) in chloroform (1 mL) was added at rt a solution of either 2,6-diformyl-4-methylphenol **2a** or 2,4-diformyl-6-methylphenol **2b** (0.164 g, 1 mmol) in chloroform (1.5 mL). The mixture was stirred at rt overnight, the solvent evaporated and the crude product crystallized from dimethylformamide **3a** or ethyl acetate–hexane **3b**.

Compound 3a: yellow crystals, mp 316–320°C, yield 80% after crystallization; ^{1}H NMR, IR and $[\alpha]_D^{20}$ spectral data are in agreement with those previously reported;[7] UV (acetonitrile) ε (nm) 7100 (345), 34200 (238); CD (acetonitrile) $\Delta\varepsilon$ (nm) −9 (362), +3 (325), −19 (275), +4 (251), +20 (234), −18 (211); UV (acidified acetonitrile) ε (nm) 45500 (451), 66600 (256), 59600 (217); CD (acidified acetonitrile) $\Delta\varepsilon$ (nm) −47 (483), +40 (440), −6 (339), −64 (285), +80 (256), −58 (228), +10 (206).

Compound 3b: yellow crystals; mp 265–270°C; yield 78% after crystallization; $[\alpha]_D^{20}$ −345 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.23–1.48 (m, 2H), 1.60–1.85 (m, 6H), 2.15 (s, 3H), 3.20–3.33 (m, 2H), 7.05 (s, 1H), 7.68 (s, 1H), 8.01 (s, 1H), 8.26 (s, 1H), 14.11 (br, 1H); IR ν (cm^{-1}) 1630; HR FAB MS (NBA matrix) *m*/*z* 727.43184 $(M+H)^+$, calcd for $C_{45}H_{55}N_6O_3$ 727.43359; UV (acetonitrile) ε (nm) 8000 (328), 82500 (242); CD (acetonitrile) $\Delta\varepsilon$ (nm) −30 (332), +43 (290), −157 (259), +183 (243), −40 (208); UV (acidified acetonitrile) ε (nm) 11900 (410), 46800 (337), 51200 (244); CD (acidified acetonitrile) $\Delta\varepsilon$ (nm) −11 (454), +64 (356), −52 (329), −18 (291), −24 (260), +30.4 (243), +9 (212), −17 (198).

4.3. Diimine 5b

A mixture of cyclohexylamine (0.198 g, 0.23 mL, 2 mmol) and 2,4-diformyl-6-methylphenol (0.164 g, 1 mmol) in toluene (10 mL) was heated under reflux for 5 h with a Dean–Stark apparatus. After cooling, the solvent was evaporated and the product was used directly; yellow oil; yield 98%; ^{1}H NMR (1:1 mixture of conformers) ($CDCl_3$) δ 1.17–1.85 (m, 40H), 2.24 and 2.28 (two singlets, 6H), 3.09–3.32 (m, 4H), 6.84 (s, 1H), 7.00 (s, 1H), 7.36 (s, 1H), 7.46 (s, 1H), 7.60 (s, 1H), 8.18 (s, 1H), 8.29 (s, 1H), 8.34 (s, 1H), 13.97 (br, 1H), 14.59 (br, 1H).

Acknowledgements

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