Chiral Iminospherand of a Tetrahedral Symmetry Spontaneously Assembled in a [6 + 4] Cyclocondensation
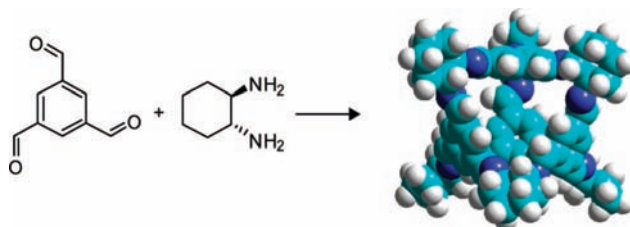
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ABSTRACT

Thermodynamically driven cyclocondensation of (*R,R*)-1,2-diaminocyclohexane and 1,3,5-triformylbenzene yields solely a [4 + 6] spherand type product. This is a unique example of spontaneous formation of an organic compound of permanent chiral tetrahedral (*T*) symmetry.

Recently, much attention has been focused on the synthesis and applications of chiral macrocyclic oligoimines derived from (*R,R*)-1,2-diaminocyclohexane (DACH) and dialdehydes.[1,2] The advantages of this type of macrocycle formation are that the reaction does not require the use of a template to preorganize the substrates and that it is highly selective, with little interference of polymer formation, when the substrates are structurally predisposed for the formation of cyclic products. The imination reaction is reversible and therefore thermodynamically driven to give the most stable products. The formation of strain-free cyclic reaction products can be realized if no significant change of the substrate conformation is necessary, as is the case in most macrocyclizations based on the imination reactions. The combination of DACH and aromatic dialdehydes is unique in providing the necessary stability of the imine bond, limited conformational flexibility of the substrates, and adequate reactivity of the system comprising of an aliphatic amine and an aromatic aldehyde. In addition, macrocyclic structure appears to stabilize the imine bonds even in the cases where both the amine and the aldehyde are aliphatic entities.[3]

Proper choice of geometry of the building blocks, i.e., DACH and dialdehyde, allows obtainment of a variety of macrocyclic oligoimines of differing shapes. The most frequently encountered polygons are triangles (trianglimines)[1a,d,4] and rhombs (rhombimines),[1b,c] while more complex structures (loopimines) can be obtained from conformationally bistable DACH derivatives.[5] Recent reports show the possibility of obtaining a nanocontainer[6a] and a nanocapsule[6b] of octahedral (*O*$_h$) symmetry as well as a chiral nanocube[6c] of *O* symmetry by dynamic covalent assembly

(1) Recent examples: (a) Gawronski, J.; Kołbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768–5773. (b) Gawronski, J.; Brzostowska, M.; Kwit, M.; Plutecka, A.; Rychlewska, U. *J. Org. Chem.* **2005**, *70*, 10147–10150. (c) Kwit, M.; Skowronek, P.; Kołbon, H.; Gawronski, J. *Chirality* **2006**, *17*, 93–100. (d) Gawronski, J.; Gawronska, K.; Grajewski, J.; Kwit, M.; Plutecka, A.; Rychlewska, U. *Chem.—Eur. J.* **2006**, *12*, 1807–1817.

(2) Review: Borisova, N. E.; Reshetova, M. D.; Ustynyuk, Y. A. *Chem. Rev.* **2007**, *107*, 46–79.

(3) Kwit, M.; Plutecka, A.; Rychlewska, U.; Gawronski, J.; Khlebnikov, A. F.; Kozhushkov, S. I.; Rauch, K.; de Meijere, A. *Chem.—Eur. J.* **2007**, *13*, 8688–8695.

(4) (a) Chadim, M.; Budĕšinsky, M.; Hodaèova, J.; Zavada, J.; Junk, P. C. *Tetrahedron: Asymmetry* **2001**, *12*, 127–133. (b) Kuhnert, N.; Lopez-Periago, A. M. *Tetrahedron Lett.* **2002**, *43*, 3329–3332. (c) Hong, B. K.; Lee, I. S.; Shin, D. M.; Chung, Y. K. *Chem. Commun.* **2004**, *n/a*, 936–937. (d) Kuhnert, N.; Göbel, D.; Thiele, C.; Renault, B.; Tang, B. *Tetrahedron Lett.* **2006**, *46*, 6915–6918. (e) Srimurugan, S.; Viswanathan, B.; Varadarajan, T. K.; Vargese, B. *Org. Biomol. Chem.* **2006**, *4*, 3044–3047. (f) Hodačova, J.; Budĕšinsky, M. *Org. Lett.* **2007**, *9*, 5641–5643.

(5) Kaik, M.; Gawronski, M. *Org. Lett.* **2006**, *8*, 2921–2924.

Scheme 1
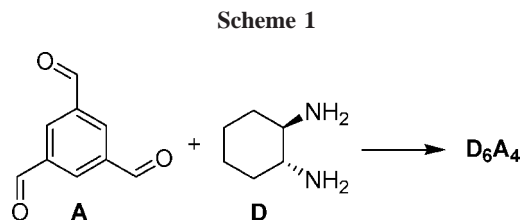
of the imine bonds from aromatic tetraaldehydes and di- or triamines.

Here, we show that DACH molecules (**D**) can react with an aromatic trialdehyde, 1,3,5-triformylbenzene (**A**),[7] to give selectively a spherand molecule in a thermodynamically driven [6 + 4] cycloimination.

The reaction of 3 equiv of **D** with 2 equiv of **A** at room temperature in dichloromethane at a concentration 0.1 M showed (TLC) the disappearance of the substrates and the formation of a single product within 12 h. Evaporation of the solvent afforded quantitatively the product having a simple ^{1}H NMR spectrum with just two sharp signals (relative intensity 1:1) in the aromatic region (δ 7.89, aromatic H, 8.16, imine H). Similarly simple was the ^{13}C NMR spectrum comprising three signals due to DACH moiety (δ 24.5, 33.1, 74.6), two aromatic region signals (δ 129.4, 136.5), and one imine signal (δ 158.9),[8] suggesting a high symmetry of the chiral product. Mass spectroscopy disclosed the molecular weight of the product (FAB M = 1116.7, MALDI TOF M + 1 = 1118), corresponding to a [6 + 4] cyclocondensation stoichiometry (Scheme 1).[9]

There are two high symmetry structures of the product which correspond to the MS data, **1** (*T*) and **2** (*D$_2$*) (Figure 1).

The tetrahedral (*T*) structure has four C_3 axes and three C_2 axes, whereas the D_2 structure has just three C_2 axes. The simplicity of the aromatic region signals in both the ^{1}H and ^{13}C NMR spectra implies the *T* symmetry of the product. D_2 symmetry would require twice as many aromatic signals in both ^{1}H and ^{13}C NMR spectra.

In order to assign a detailed structure of the product of cyclocondensation, we calculated the low energy conformers of **1** and **2** using the semiempirical PM3 method.[10]

Figure 1. Schematic structures of **D$_6$A$_4$** spherand.

The calculated structures of **1** and **2** are characterized by a nearly flat conjugated aromatic triimine system, a trans configuration of the imine bond, and a nearly eclipsed position of the imine bond with regard to the C*−H bond in an undistorted cyclohexane skeleton, as previously found for unstrained imine polygons[1a,b] (Figure 2).

Calculated heats of formation and free energies of **1** and **2** show that structure **1** is significantly more stable than **2** (Table 1). One of contributing factors to preferential formation of **1** under thermodynamic conditions is its higher symmetry (symmetry number for **1** is 12, for **2** is 4). Consequently, there is entropy of symmetry advantage of the order of 0.66 kcal·mol^{-1} for the formation of **1** at room temperature. An additional factor contributing to destabilization of structure **2** is a larger (−28°) H−C*−N=C torsion angle of two of the six imine bonds connected with nonplanarity of the aromatic imine system; see the Supporting Information.

Table 1. Calculated Differences of Heats of Formation (HOF), Free Energy (ΔE), and Entropy of Symmetry at 298 K (S_{sym})

structure	HOF (kcal·mol^{-1})	ΔE (kcal·mol^{-1})	S_{sym} (kcal·mol^{-1})
1	0	0	0.66
2	3.4	4.3	0

Since the product of cyclocondensation of **D** and **A** is chiral, we were able to obtain the final proof of its structure by

(6) (a) Liu, X.; Liu, Y.; Li, G.; Warmuth, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 901–904. (b) Liu, X.; Liu, Y.; Warmuth, R. *Chem.—Eur. J.* **2007**, *13*, 8953–8959. (c) Xu, D.; Warmuth, R. *J. Am. Chem. Soc.* **2008**, *130*, 7520–7521.

(7) Fourmigue, M.; Johannsen, I.; Boubekeur, K.; Nelson, C.; Batail, P. *J. Am. Chem. Soc.* **1993**, *115*, 3752–3759.

(8) A 81 mg (0.5 mmol) portion of 1,3,5-triformylobenzene dissolved in 2 mL of CH$_2$Cl$_2$ was added to 85 mg (0.75 mmol) of (*R,R*)-1,2-diaminocyclohexane in (3 mL) CH$_2$Cl$_2$ to give a clear solution. After 12 h at room temperature, the product partially crystallized. The solution was evaporated to dryness to give a product in quantitative yield, pure by NMR. The product can be crystallized from CHCl$_3$/hexane as an amorphous powder: mp > 360 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1−2 (m, 24H), 3.3 (bs, 12H), 7.9 (s, 12H), 8.1 (s,12H); ^{13}C NMR (75 MHz, CDCl$_3$, TMS) δ 24.5, 33.1, 74.6, 129.4, 136.5, 158.9; IR (KBr cm^{-1}) 2927, 2857, 1648, 1599, 1448, 1370, 1340, 1154, 1091, 898, 942, 884, 863, 691, 669, 518, 477, 438; CD (CH$_2$Cl$_2$/MeCN, 1:9) ($\Delta\varepsilon$, λ (nm)) 58.1 (266), −49.2 (262), 53.2 (239), 12.4 (221), 18.8 (215); UV (ε, λ (nm)) (CH$_2$Cl$_2$/MeCN, 1:9) 24520 sh (261), 63750 (241).

(9) Note that the simplest D$_3$A$_2$ (barrel-type) product cannot be accommodated in a strain-free structure.
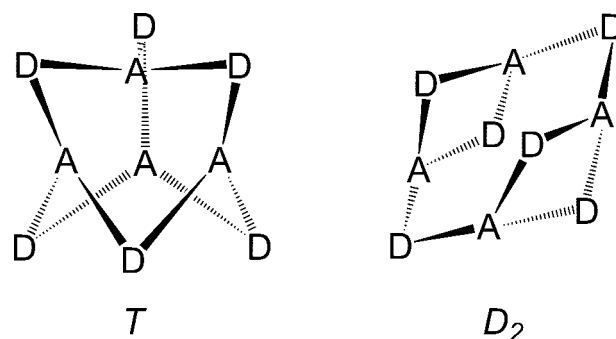
(10) *Gaussian 03, Revision C.02*: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; 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.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.
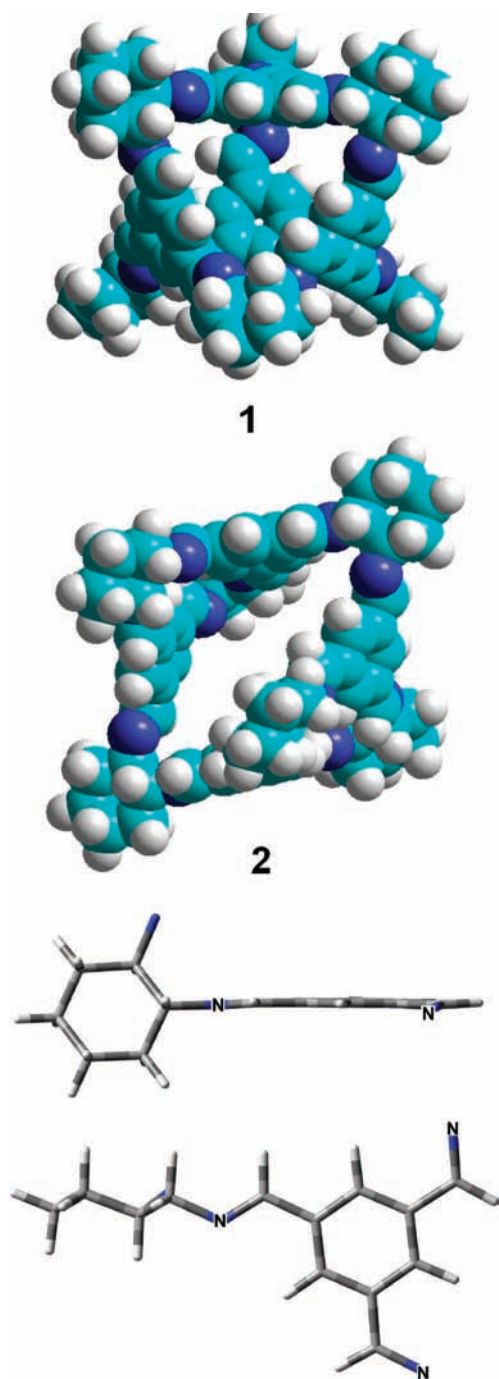
Figure 2. Calculated structures **1** and **2** of **D₆A₄** spherand and a detailed view of the imine bond conformation.

comparing the experimental circular dichroism spectrum of **D₆A₄** with the computed CD spectra for **1** and **2** based on their calculated structures.[11] The CD spectra were calculated using TDDFT method at B3LYP/cc-pvdz level using 150 lowest energy transitions. To save computation time, the cyclohexane rings in structures **1** and **2** were removed by substituting the C−N bonds with the H−N bonds. Since the cyclohexane ring

(11) Although the product could be crystallized, no X-ray quality crystals were obtained.
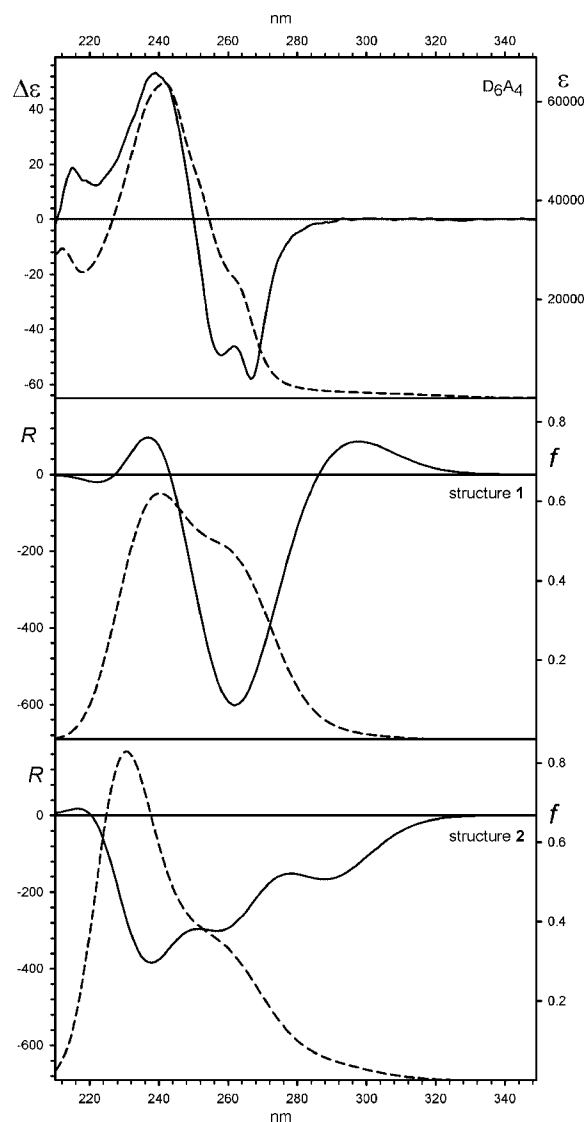
Figure 3. CD (solid line) and UV (dashed line) experimental spectra for **D₆A₄** and calculated spectra for **1** and **2**. The calculated UV maxima of **1** and **2** are blue-shifted by 10 nm for a better match with the experimental UV maximum of **D₆A₄**.

is nonchromophoric, its contribution to the UV/CD spectrum is expected to be insignificant. Note that despite the assumed approximation the calculation reproduces very well basic features of the UV absorption spectrum. As shown in Figure 3, the intense $\pi-\pi^*$ absorption bands of the benzene-1,3,5-triimine system at ca. 260 and 240 nm in **D₄A₆** are associated with intense, presumably exciton-type Cotton effects (−/+) at these wavelengths. A similar (−/+) CD band pattern is calculated for **1** (negative at ca. 260 nm and positive at ca. 240 nm); however, a very different CD spectrum was obtained for **2** (a series of negative Cotton effects between 320 and 220 nm). Since the CD spectra are sensitive to chiral molecular structure, the calculation results confirm that **D₆A₄** product has a spherand structure of unique tetrahedral (*T*) symmetry **1**.[12]

According to a recent review[13] compounds of *T* symmetry are extremely rare, the best known examples being

metallacyclic polygons reported by Stang et al.[14] Product **D₄A₆** is apparently the first example of structurally characterized covalently bound molecule of chiral tetrahedral symmetry.[15]

The uniqueness of the cyclocondensation of **D** and **A** is demonstrated by the results of cyclocondensation of **A** with (R,R)-1,2-diamino-1,2-diphenylethane, having a more flexible structure. A mixture of products was obtained in this reaction, and no cyclic structures could be detected by MS and NMR analysis.

In summary, we have demonstrated that the first chiral iminospherand of a tetrahedral symmetry could be obtained in a simple [6 + 4] cyclocondensation of DACH and 1,3,5-triformylbenzene with very high yield, using no template or special reaction conditions. The direction of this unique reaction is highly biased by structural factors and the symmetry of the product, in which tripodal triiminebenzene units form the vertices and DACH molecules are the sides of the tetrahedron. While the spherand reported here is not large enough to accommodate other molecules in its cavity, work is now in progress to obtain larger entities, based on the principles of structure planning described above.

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(12) It should be noted that an irreversible condensation of DACH with benzene-1,3,5-tricarboxylic acid trichloride has led to a product with a structure similar to that of **2**, with a low yield. (a) Yoon, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 823–824. (b) Yoon, S. S.; Still, W. C. *Tetrahedron Lett.* **1994**, *35*, 2117–2120.

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(14) (a) Stang, P. J.; Olenyuk, B.; Muddiman, D. C.; Wunschel, D. S.; Smith, R. D. *Organometallics* **1997**, *16*, 3094–3096. (b) Stang, P. J.; Olenyuk, B. *Handbook Nanostruct. Mater. Nanotechnol.* **2000**, *5*, 167–224.

(15) A tetrahedral receptor has been prepared from trimesic acid and chiral 1,2-diamines in a multistep synthesis; however, no structure characterization has been reported: (a) Yoon, S. S.; Still, W. C. *Tetrahedron Lett.* **1994**, *35*, 8557–8560. Achiral tetrakis(trimethylsilyl)tetrahedrane has recently been synthesized: (b) Maier, G.; Neudert, J.; Wolf, O.; Pappusch, D.; Sekiguchi, A.; Tanaka, M.; Matsuo, T. *J. Am. Chem. Soc.* **2002**, *124*, 13819–13826.