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Unprecedented Selectivity in the Formation of Large-Ring Oligoimines from Conformationally Bistable Chiral Diamines

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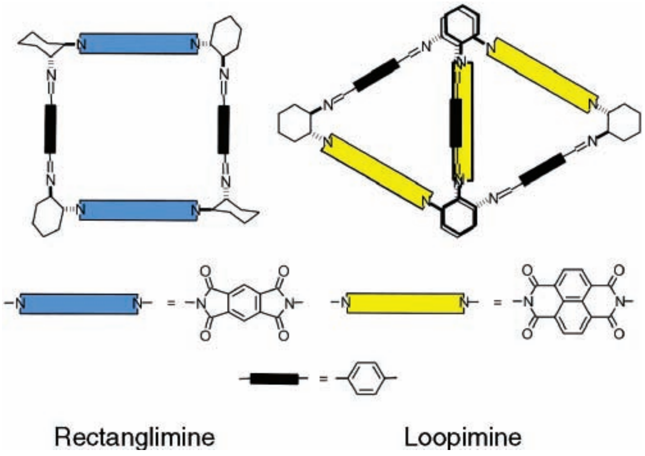
ABSTRACT



Stereoselective formation of large macrocycles in "click-type" reactions is a current challenge. Chiral macrocycles of differing size and shape (e.g., rectanglimine or loopimine) were selectively obtained by cyclocondensation of terephthalaldehyde or isophthalaldehyde with conformationally bistable chiral diamines derived from *trans*-1,2-diaminocyclohexane and aromatic dianhydrides. This opens new opportunities for the programmed synthesis of large-ring molecular assemblies.

The synthesis of noncollapsible macrocycles has recently received wide attention stimulated by their anticipated applications related to asymmetric synthesis (ligands, organocatalysts) and nanoscale patterning in materials and biomolecular sciences. Whereas all-carbon macrocycles (annulenes) are appealing due to their structural elegance, their synthesis frequently represents a formidable challenge due to the number of synthetic steps, reaction yields, and conditions. This is best illustrated by the recent development of synthetic methodology for cyclic phenylene ethynylene oligomers[1] which, however, does not rely on "click-type" chemistry.[2]

Cyclooligomerization through reversible imine bond formation provides macrocyclic heteraphanes of diverse structures and functionalities, essentially in one step and in high yields. Recently, we and others have developed routes to chiral macrocyclic derivatives of enantiomerically pure *trans*-

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1,2-diaminocyclohexane (DACH) through its [3 + 3] cyclocondensation with dialdehydes to yield trianglimines[3−8] or calixsalens.[9−10] The cases of preferable [2 + 2] cyclocondensation of DACH with 1,3-aromatic dialdehydes[5b,8,11,12] or dialdehydes derived from diphenylmethane[13] are also known, and rhomb-shaped imines were obtained from ether-linked aromatic dialdehydes.[14] In addition, [3 + 3] cyclocondensation products were obtained from aromatic dialdehydes and 1,2-diaminobenzene (DAB) derivatives.[15,16] Stoddart has used the reversible nature of imine bond formation for the synthesis of rotaxanes, catenanes, and hemicarcerands.[17]

The clue to successful macrocyclization, as opposed to linear oligomer formation, is predisposition of the reactants to form a strain-free macrocyclic product in a reversible reaction. The synthetic strategy of the imine cyclocondensation is based on the use of cyclic substrates to form macrocycles from small cycles. Cyclic substrates (here the dialdehydes and DACH or DAB) are conformationally restricted, and so are the intermediates of their condensation.

We reasoned that adding discrete conformational states of the chiral diamine would lead to more structurally diversified macrocyclic oligoimines. With DACH, triangular products are formed as a consequence of the two equatorial C−N bonds projecting at a 60° angle from the apexes of the triangle. When two DACH molecules are joined together in such a way that the two connecting C−N bonds are collinear, two structures, *C* and *S*, of close energies are obtained (Figure 1).[18] The two DACH molecules can be collinearly joined for example by a diimide molecule.[19]

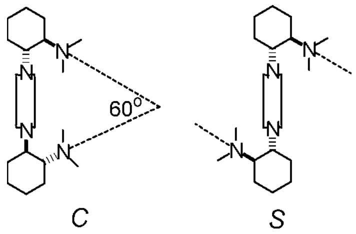

Figure 1. Two conformers of a chiral diamine consisting of two molecules of (*R*,*R*)-1,2-diaminocyclohexane connected by a diimide bridge.

In the *C*-shaped conformer, the two external C−N bonds are noncoplanar and project at 60°, whereas in the *S* conformer their directions are antiparellel. It is obvious that condensation of the *S* conformer of the diamine with linear dialdehyde would lead to no macrocyclic product, regardless the number of molecules involved. For the *C* conformer, [1 + 1] cyclocondensation with a dialdehyde would lead to a strained product, whereas [2 + 2] cyclocondensation would be perfectly feasible. More intriguing are the opportunities provided by mixing *S* and *C* conformers of the diamine in a cyclic oligoimine product. On purely geometrical grounds, cyclic product formation would require the torsion (or dihedral) angles around the cycle to sum up to zero. Since the dihedral angle between the external N−C···C−N bonds is −60° in the *C* conformer and 120° in the *S* conformer (Figure 1), macrocycle formation would be feasible with the participation of two *C* and one *S* conformer of the diamine in a condensation with a linear dialdehyde. Note that no simple trianglimine macrocycle can be formed with either *C* or *S* conformer of the diamine. We therefore set out to explore the products formed with the participation of the two conformers of a diamine in an equilibrium.

The requisite diamines, **1** and **2**, were obtained (as their *p*-toluenesulfonate salts) following our procedure for monoprotection of DACH by its condensation with anhydrides of aromatic dicarboxylic acids.[20] Thus, the condensation of 2 equiv of (*R*,*R*)-DACH with 1 equiv of either 1,4,5,8-naphthalenetetracarboxydianhydride or 1,2,4,5-benzenetetracarboxydianhydride (pyromellitic dianhydride) in boiling acetic acid or DMF in the presence of 2 equiv of *p*-toluenesulfonic acid gave the products, **1** and **2**, respectively, in yields 86−87%. The ^{1}H NMR spectrum of **1** shows two singlets and two doublets due to the protons of the diimide core,[18] corresponding to *C* and *S* conformers in the ratio 1:2. The *S* conformer is favored in the equilibrium since electrostatic repulsions of the ammonium groups destabilize more strongly the *C* conformer. Indeed, when **1** was converted to **3**,[21] *C* to *S* population was found very close to equal, from the integration of the imide proton signals.[22]

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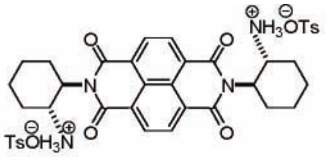

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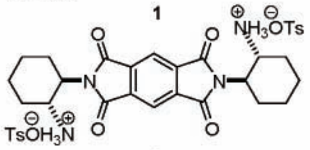

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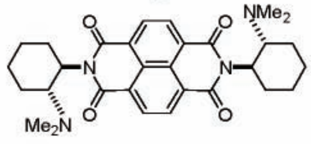

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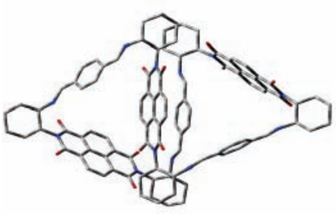

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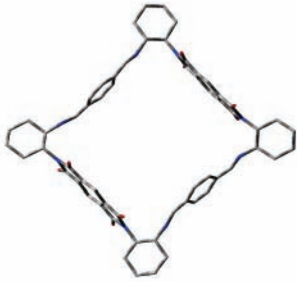

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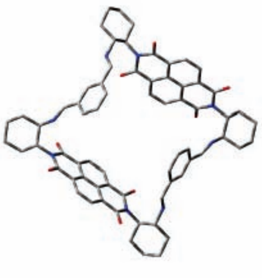

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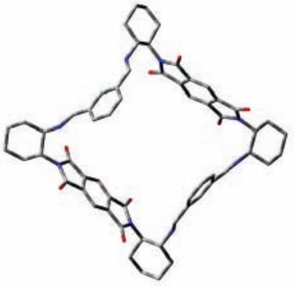

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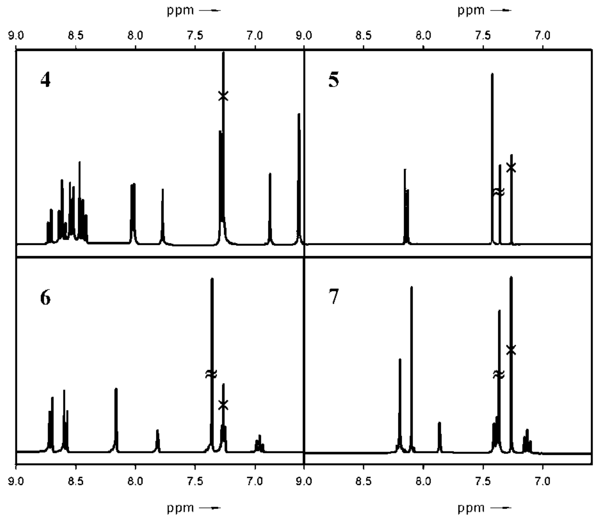

Figure 2. Aromatic region of the ^{1}H NMR spectra of macrocycles **4**−**7** ($CDCl_3$ peak marked with × and C_6H_6 peak marked with ≈).

Condensation of **1** or **2** with either terephthalaldehyde or isophthalaldehyde in the presence of NEt_3 in CH_2Cl_2 solution at room temperature gave, after crystallization, the main product in yields of 82% (**4**), 78% (**5**), 80% (**6**), and 65% (**7**). The structures of these products were deduced from the analysis of their MS, NMR, and CD spectra. Surprisingly, [3 + 3] cyclocondensation product **4** (*m*/*z* 1676) was obtained from **1** and terephthalaldehyde, whereas the same dialdehyde and **2** furnished [2 + 2] cyclocondensation product **5** (*m*/*z* 1016). The clue to the structure of **4** was the presence of separate ^{1}H NMR signals due to the diimide protons of *C* and *S* structures in a ratio of 2:1 (Figure 2).

Diimide proton signals in the *C* fragments form four partially overlapping doublets (δ 8.40−8.75), whereas a pair of singlets located at δ 7.78 and 8.47 is assigned to the *S* structure. Separate signals in the 2:1 ratio were also observed for the imine CH (singlets at δ 6.63 and 6.88), 1,4-phenylene ring (doublets at δ 7.29 and 8.03 as well as at δ 8.40−8.70), and cyclohexane CH-imide (dt at δ 5.20 and 5.30) protons.[23] The signals of the imine CH protons were significantly shifted upfield due to the deshielding effect of the nearby naphthalenediimide groups. These observations are consistent with the structure **4** of C_1 symmetry obtained by molecular modeling with the PM3 method (see also the Supporting Information). The structure is rigid, of loop type (hence *loopimine*), made by two intertwined triangular structures. Note that in order to maintain a syn arrangement of the imine CH and cyclohexane CH bonds in such a structure the diimine fragment located centrally is in a cis conformation, as opposed to the two other trans diimine fragments.[24]

In accordance with the D_2 symmetry of [2 + 2] cycloaddition product **5** (*m*/*z* 1016), its ^{1}H NMR spectrum (Figure 2) is quite simple, consisting of two singlets at δ 8.14 and 8.15 due to the imide and imine CH protons and one singlet at δ 7.42 of the 1,4-phenylene protons. There are 15 lines in the ^{13}C NMR spectrum—six due to the cyclohexane, six (including two of the carbonyl groups) due to pyromellitic diimide, and three due to the diimine carbon atoms. The molecule uses two pyromellitic diimide fragments in a *C* conformation to form a rectangular structure **5** (*rectanglimine*).

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(21)) We note that **3** and its congeners (**4** and **6**) are red (broad and weak absorption at 480 nm, ϵ 500). This is evidently due to the presence of the amino group in the close vicinity of the carbonyl group, allowing for n(donor)−π*(acceptor) electronic transition (cf. Kwit, M.; Gawroński, J. *Mendeleev Commun.* **2003**, 139).

(22)) Imide proton signals of **2** were not resolved due to the higher rate of exchange of *C* and *S* conformers at ambient temperature.

(23)) The positions of the cyclohexane C**H**N signals can be calculated using the corrected values $\Delta\delta$ due to the arylimine substituent, i.e., $\Delta\delta_{H\alpha} = 0.6$, $\Delta\delta_{H\beta} = 0.6$. The values reported originally for this substituent (ref 20) were miscalculated from the data for symmetrical DACH diimine derivatives.

(24)) The structure of **4** is very unique; we were able to find in the literature a related loop structure of 1,2,5,6,9,10,13,14-tetrabenzo-3,7,11,15-tetradehydro[16]annulene which was formed as a trace product in a Stephens−Castro coupling of copper(I) *o*-iodophenylacetylide: (a) Campbell, I. D.; Eglington, G.; Henderson, W.; Raphael, R. A. *Chem. Commun.* **1966**, 87−89. (b) Solooki, D.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J.; See, R. F.; Churchill, M.; Ferrara, J. D. *J. Organomet. Chem.* **1994**, *470*, 231−236.

In the case of isophthalaldehyde products of [2 + 2] cyclocondensation, **6** (*m*/*z* 1118) or **7** (*m*/*z* 1016) were obtained from either diamine **1** or diamine **2**, accordingly. Their ^{1}H NMR spectra show one set of signals due to 1,3-phenylene groups (one triplet, one doublet, and one singlet), one singlet due to imine CH and two doublets (in the case of **6**), or one singlet (in the case of **7**) due to imide protons (Figure 2). Thus, in both molecules the imide fragments are in a *C* conformation. Molecular modeling shows that both **6** and **7** molecules assume a low energy saddle-shaped C_2 symmetry conformation (see the Supporting Information).

Macrocycles **4**−**7** are characterized additionally by strong Cotton effects in their CD spectra (Figure 3).

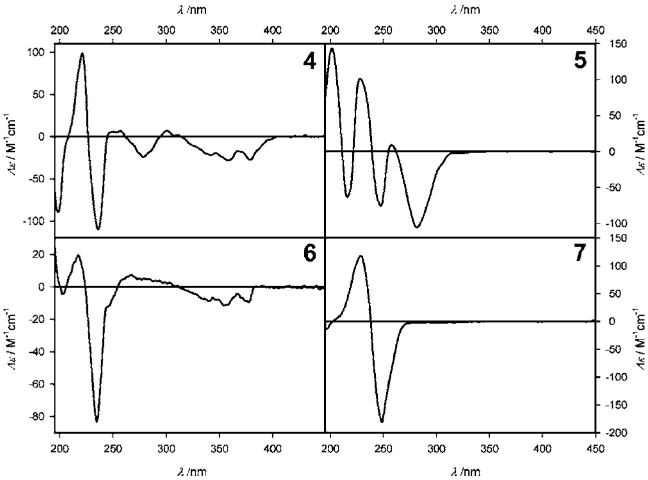

Figure 3. CD spectra of macrocycles **4**−**7** recorded in acetonitrile solution.

The Cotton effects are generated by exciton coupling of the allowed transitions of the neighboring aromatic diimine and diimide chromophores (see the Supporting Information). Most characteristic are negative Cotton effects in the range 310−400 nm, due to the coupling of the long axis polarized transitions of the naphthalenediimide chromophores in **4** and **6**.

Strong negative exciton Cotton effects are also seen between 220 and 250 nm in these molecules, originating from the coupling of short axis polarized transitions (located at 235−240 nm) of the diimide chromophores. In the case of **5** and **7**, the coupling of long axis polarized transitions of the pyromellitic chromophores, localized at around 240 nm, plays a dominant role. In the case of **7**, the pyromellitic transition at 240 nm is additionally coupled to the 1,3-benzenediimine transition at 236 nm, resulting in a very strong exciton Cotton effect ($A = -300$). The negative sign of the Cotton effects of **4**−**7** reflects negative helicity of these assemblies, determined by the absolute configuration of the component DACH molecules.

In summary, we demonstrated that cyclocondensation of conformationally bistable chiral diamines **1** and **2** with aromatic dialdehydes affords cyclic oligoimines of varying ring size and shape. While the foundations of selectivity in ring formation under thermodynamic conditions in the cases reported here are not yet known, we note that the outcome of the macrocycle synthesis may depend on the exact size of the component molecules (in this case, the distance from nitrogen to nitrogen atom in diimide and diimine spacers), as well as their valence and torsion angles. An additional important factor is the availability of a limited number (here two) of conformers of close energy, of which one is better suited to provide the low energy macrocycle structure. Work is now in progress to determine the scope, conditions, and limits of such macrocyclization reactions.

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Supporting Information Available: General procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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