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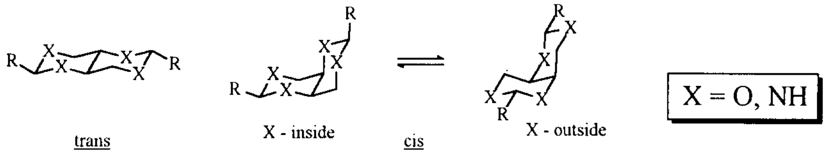
A New Class of Heterobicyclic Systems: Dioxadiazadecalins[1]

Alexander Star, N. Gabriel Lemcoff, Israel Goldberg and Benzion Fuchs*

School of Chemistry (Raymond and Beverly Sackler Faculty of Exact Sciences),
Tel-Aviv University, Ramat-Aviv, 69978 Tel-Aviv, Israel

Abstract. Two entirely new, fused di(oxazane) heterocycles, the diastereomeric 1,5-dioxa-3,7-diazadecalin (DODAD) and 1,5-diaza-3,7-dioxadecalin (DADOD) systems (**3**, **4**, **6** and **7**) were prepared and probed, both experimentally and computationally. The enantiopure 2,6-di(p-nitrophenyl)-*cis*-DODAD and -*cis*-DADOD derivatives (**10**, **11**) underwent X-ray analysis.

We have been pursuing recently[1,2] the construction and study of new types of macrocyclic systems built on 1,3,5,7-tetraheterodecalin (THD)† (Scheme 1) core molecules in their *trans* or *cis* configuration (with the latter's two possible forms, "X-inside" and "X-outside"). Oxygen (X=O) 1,3,5,7-tetraoxadecalin (TOD)[2] diacetal systems were the first to be studied followed by the nitrogen (X=NH) tetraazadecalin (TAD)[1] diaminal analogues, with particular attention to their stereoelectronic[3] features and propensity for metal ion inclusion.[2c,d]



Scheme 1. The diastereoisomeric 1,3,5,7-tetraheterodecalin molecular species.

We report now the entirely novel types of tetraheterodecalin systems, namely *trans*- and *cis*-1,5-dioxa-3,7-diazadecalin (DODAD) and -1,5-diaza-3,7-dioxadecalin (DADOD)†. Thus (Scheme 2), *cis*-DODAD (**3**) and *cis*-DADOD (**6**) and substituted derivatives were prepared from the respective *threo-L*-1,4-diamino-2,3-butanediol (**1**) and *threo-D*-2,3-diamino-1,4-butanediol (**2**). **1** was secured by existing methods[4] and **2**, by improved procedures[4a,5], both starting from *L*-tartaric acid. The reaction of *meso* starting materials with various aldehydes gave corresponding *trans* diastereomers **4** and **7**.

Reaction of **1** with formaldehyde in water at and below room temperature gave a kinetic product in 30% yield, identified as the tricyclic compound (**5**), which is evidently formed via the 5,5'-bi(oxazolidinyl) primary product (Scheme 2). At higher temperatures and optimally at pH 3, the thermodynamic product *cis*-DODAD **3** could be isolated in 75% yield. The reaction of **2** with aqueous formaldehyde was even faster to yield 3,3'-methylene-4,4'-bi(oxazolidinyl) (**8**), apparently by a similar kinetic route. However, by using an excess of **2** at higher temperatures (~100^{0}C) and low pH, *cis*-DADOD **6** was obtained in ratio 1:1 with **8**, each in 20% yield.

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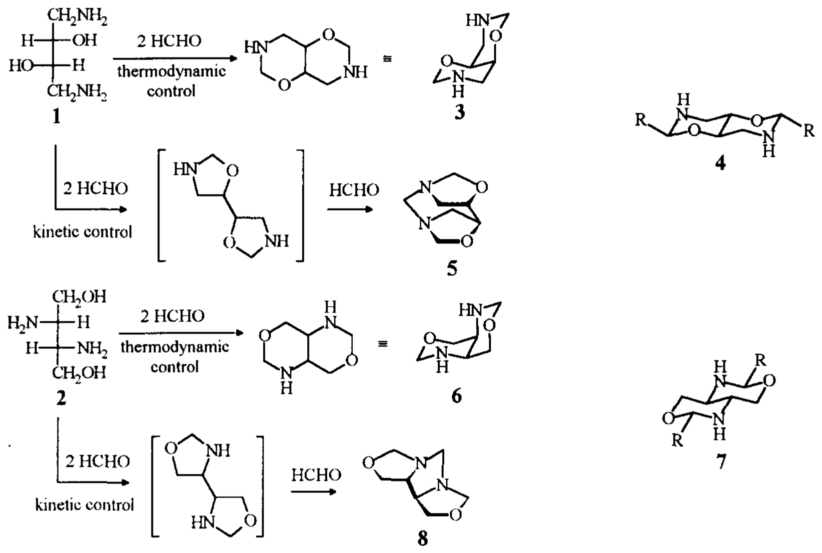
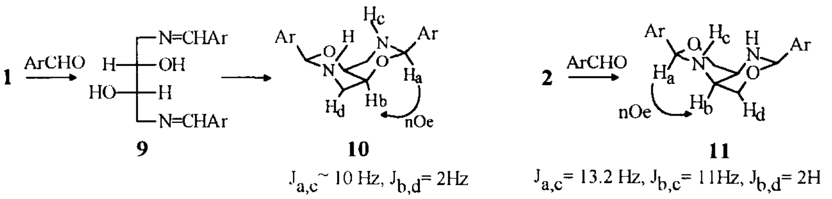
† Due to a minor but basic omission in the CIP rules, one must use 9,10-helicity to assign configuration to chiral dissymmetric *cis*-decalin systems. Thus, **10** is (2*R*,6*R*, 9*S*,9,10-*P*)-2,6-di(p-nitrophenyl)-*cis*-1,5-dioxa-3,7-diazadecalin.



Scheme 2. The reactions of 1,2,3,4-diaminobutanediols with aldehydes and their stereospecific products.

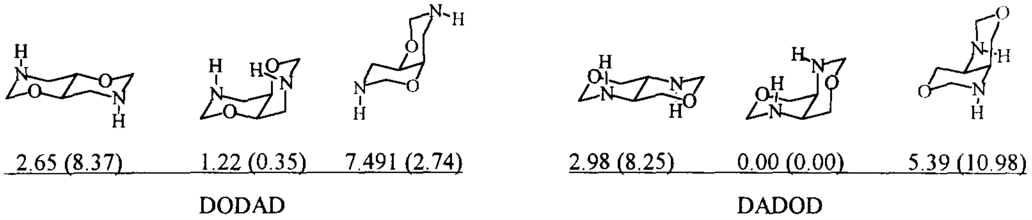
In the reaction of **1**.2HCl with 4-nitrobenzaldehyde (Scheme 3) and aqueous K_2CO_3, the stable Schiff base 1,4-di(p-nitrobenzaldimino)-2,3-butanediol **9** was immediately formed and isolated in crystalline form (various electron-poor aryl aldehydes behaved similarly). Acid catalysed ring closure of **9** in refluxing methylene chloride gave 2,6-di(nitrophenyl)-DODAD **10** in quantitative yield. This happened also, albeit slower, in the solid state. The ring-chain tautomerism in 1,3-oxazines has been thoroughly and illuminatingly studied[6] and is observed in the *cis*-DODAD series, as well. The 2,6-diaryl systems with substituents of higher Hammett σ values show higher DODAD/Schiff base ratios[6], the tautomeric equilibria in case of Ar=p-nitrophenyl being almost completely shifted to DODAD (**10**). Notably, in the reactions with aromatic aldehydes only 2,6-aryl substituted cis-DODAD systems were isolated and no five-membered (oxazolidine) products were observed, in agreement with previous observations[6c]. At the same time, the DADOD derivative (**11**) was obtained directly from **2** with p-nitrobenzaldehyde in water at room temperature, within 18 hrs (90%), with no apparent Schiff base intermediacy.



Scheme 3. 2,6-Diaryl *cis*-DODAD and -DADOD compounds (N,Oinside). In **9**, **10** & **11**, Ar = *p*-nitrophenyl.

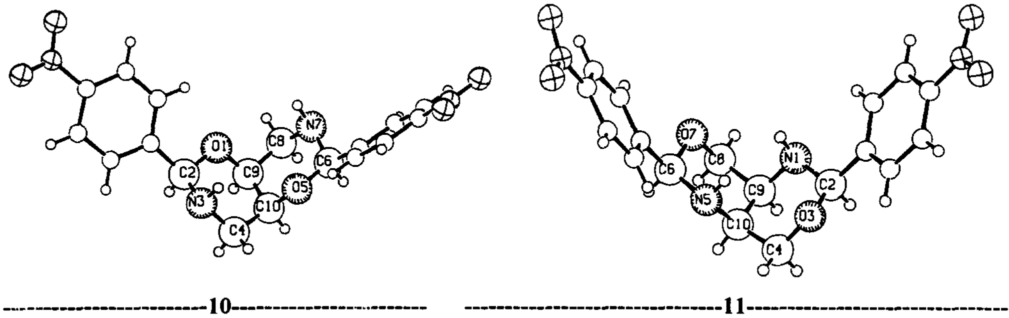
NMR (nOe, ^3J) measurements provided clear evidence that compounds, **3**, **6**, **10** and **11** are N,O-inside forms with axial N-H (Schemes 2 & 3); thus, the small vicinal coupling constants of the 4_{ax},10 hydrogens (as also in the O-inside forms in the TOD series[2]) exclude an *anti* relationship.

Some of these experimental results are of stereoelectronic origin. The *anomeric effect*[3] in O-C-O[3a,b], N-C-N[3c,d] and O-C-N[3e,f] containing systems is well known. The O-C-N anomeric unit is outstanding, since it incorporates a good donor (N) adjacent to an excellent acceptor (O). Hence, in our systems, conformers having an N-lone-pair (lp) antiperiplanar to the adjacent C-O bond (H-N axial) are bound to exhibit enhanced stability, due to the postulated delocalization of the N-lp into the adjacent $\sigma^*_{c\text{-}o}$ orbital. We caculated DODAD and DADOD using the MM2 force field (earlier reparametrized for the *anomeric effect* (MM2-AE) in all above X-C-Y moieties[3b-f]) and MM3 (recently reparametrized for the *gauche effect* (MM3-GE)[2b] in O-C-C-O systems). These emulated well the axial H-N and the energetic preference for the N,O-inside conformations (Scheme 4).



Scheme 4. Relative energies (in kcal/mol) of *trans* and *cis* DODAD and DADOD in their most stable ring- and N-H (diaxial) conformations, as calculated by MM2-AE (MM3-GE).

Both *cis*-2,6-di(p-nitrophenyl) compounds (**10**, **11**) were submitted to single crystal X-ray diffraction analysis (Figure 1)[7] for ultimate structural definition; some relevant geometry details are shown below.



10

O1-C2	1.424	N3-C4	1.472	O1-C2-N3-C4	57.6
O1-C9	1.438	C4-C10	1.517	N3-C4-C10-O5	-74.7
C2-N3	1.424	C9-C10	1.527	C6-O5-C10-C4	176.3
				O1-C9-C10-O5	71.9

11

N1-C2	1.433 (1.431)	O3-C4	1.423 (1.417)	N1-C2-O3-C4	57.8 (-59.4)
N1-C9	1.454 (1.482)	C4-C10	1.525 (1.524)	O3-C4-C10-N5	67.5 (71.0)
C2-O3	1.444 (1.403)	C9-C10	1.497 (1.535)	C6-N5-C10-C4	-172.5 (-169.6)
				N1-C9-C10-N5	-68.5 (-70.2)

Figure 1. ORTEP drawings from the X-ray analyses of (2*R*,6*R*,9*S*; 9,10-*P*)-*cis*-2,6-di(p-nitrophenyl)-1,5-dioxa-3,7-diazadecalin (**10**) and (2*S*,6*S*,9*R*; 9,10-*M*)-*cis*-2,6-di(p-nitrophenyl)-1,5-diaza-3,7-dioxadecalin (**11**), along with selected structural parameters (bond lengths in Å and torsion angles in deg).[7]

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7. a) Crystal data for **10**: $C_{18}H_{18}N_4O_6$, formula weight 386.36, orthorhombic, space group $P2_12_12_1$, a = 6.210(3), b = 6.905(1), c = 41.084(5) Å, V = 1761.7(9) Å^3, Z = 4, D_{calc}=1.457 g.cm^{-3}, F(000) = 808, μ(MoKα) = 1.17 cm^{-1}, 1954 unique reflections, R = 0.054 for 1369 observations with $F_0 > 4\sigma$ (F_0) and R = 0.094 for 1954 unique data; at convergence, S = 1.30 and $|\Delta\rho| \leq 0.19$ e.Å^{-3}.[8]

   b) Crystal data for **11**: $C_{18}H_{18}N_4O_6$, formula weight 386.36, monoclinic, space group $P2_1$, a = 6.264(3), b = 22.663(3), c = 12.816(2) Å, β = 93.06(2)°, V = 1816.8 Å^3, Z = 4, D_{calc}=1.413 g.cm^{-3}, F(000) = 808, μ(MoKα) = 1.08 cm^{-1}, 2213 unique reflections, R = 0.074 for 1293 observations with $F_0 > 4\sigma$ (F_0) and R = 0.12 for 2213 unique data; at convergence, S = 0.97 and $|\Delta\rho| \leq 0.28$ e.Å^{-3}.[8] There are two molecules in the asymmetric unit, differing in various structural details. The final results are characterized by a relatively low precision, due to the low data-to-parameters ratio in this case.
8. Atomic coordinates, bond lengths and angles, torsion angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.

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