Mechanism of Formation and Stabilities of the New Dioxadiazadecalin Systems. Ring−Chain Tautomerism[1]

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A linear free energy relationship study is presented for the reactions of *threo*- and *erythro*-1,4-diamino- and -2,3-diaminobutanediols (**1**, **2**) with six *p*-substituted benzaldehydes, the end products of which are the novel *cis*- and *trans*-1,5-dioxa-3,7-diazadecalin (DODAD, **7***ci*, **7***tr*) and -1,5-diaza-3,7-dioxadecalin (DADOD, **8***ci*, **8***tr*) systems. The consecutive double 1,3-oxazane ring closures take place mostly via Schiff bases and are moderately polar ring−chain tautomeric reactions with low positive ρ-values (0.69) affected by steric strain, stereoelectronic effects, and intramolecular hydrogen bonds. These are relatively slow processes, which may occur in the solid as well, but are greatly enhanced by acid catalysis.

Introduction

In the quest for novel supramolecular host compounds, we have recently been exploring the 1,3,5,7-tetraheterodecalin system (**THD**) (Scheme 1) and have already described significant results in the tetraoxadecalin (**TOD**, X = Y = O)[2] and tetraazadecalin (**TAD**, X = Y = NH)[3] series. Recently we reported[4] the new 1,5-dioxa-3,7-diazadecalin (DODAD) and 1,5-diaza-3,7-dioxadecalin (DADOD) systems (Scheme 1), which we have prepared by acid- promoted condensation of formaldehyde with 1,4-diamino-2,3-butanediol (**1**) or 2,3-diamino-1,4-butanediol (**2**), respectively. The reactions are fully stereospecific, i.e., *threo*-**1** or **2** provides with aldehydes *cis*-DODAD or -DADOD and *erythro*-**1** or **2** leads to *trans*-DODAD or -DADOD systems, respectively. Indeed, the *meso* character of, e.g., *erythro*-**1***m* is preserved in the centrosymmetric (*Ci*) *trans*-DODAD (**7***tr*), while the (C_2) axial symmetry of the *threo*-**1***t* is preserved in the *cis*-DODAD (**7***ci*) product; similar results are found for the DADOD series. For the *cis* configuration, it should be mentioned that of the two interconverting (by ring inversion or ring−chain tautomerism) forms[4] (Scheme 1), the X,Y-inside diastereoisomer is the most stable one.

The products of the reaction of amino alcohols with aldehydes exist as ring−chain tautomeric mixtures of 1,3-O,N-heterocycles and the corresponding Schiff bases (Scheme 2); these systems have been studied in detail in the Fülöp−Bernáth, Pihlaja, and Riddell groups.[5−7] In these processes, according to Baldwin's rules,[8] the *endo-trig* type ring-closure reaction should be favored for 1,3-oxazanes (tetrahydro-1,3-oxazines) (*6-endo-trig*), but disfavored for oxazolidines (*5-endo-trig*).

For 2-aryl-substituted saturated 1,3-O,N-heterocycles, the ring−chain tautomeric process has been analyzed[5,6a] using the Hammett equation: $\log K = \rho\sigma^+ + \log K_0$, where K = [ring]/[chain], σ^+ is the Hammett−Brown constant of the 2-aryl substituent, and the slope ρ is a characteristic of the ring system. A ρ value of 0.76 ± 0.04 has been found[5,6a] for regular 1,3-oxazanes in $CDCl_3$ solution at room temperature, which gets lower at higher temperatures[6c] or for multicomponent tautomeric mixtures[7a] (both affecting the entropy term) (vide infra).

With the DODAD and DADOD systems being fused 1,3-oxazanes, we felt compelled to subject them to a ring−chain LFER analysis, to assess the relative stability of the intermediate and final products, and to understand the steric and electronic factors in their synthesis and behavior. These interrelationships are also of considerable interest in the context of the diastereomeric starting 1,2,3,4-diaminobutanediols and their derivatives and complexes, which had received attention for their enhanced anticancer properties[9a−c] and, in particular the dissymmetric (C_2) ones, as HIV protease inhibitors.[9d]

Results and Discussion

Following our initial findings[4] and avoiding acid conditions, Schiff bases could be observed and we proceeded

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(1) New Supramolecular Host Systems, part 10. (a) For part 9, see: Reany, O.; Goldberg, I.; Abramson, S.; Star, A.; Golender, L.; Ganguly, B.; Fuchs, B. The 1,3,5,7-Tetraazadecalins. Theory *vs* Experiment. *J. Org. Chem*. **1998**, *63*, 8850.

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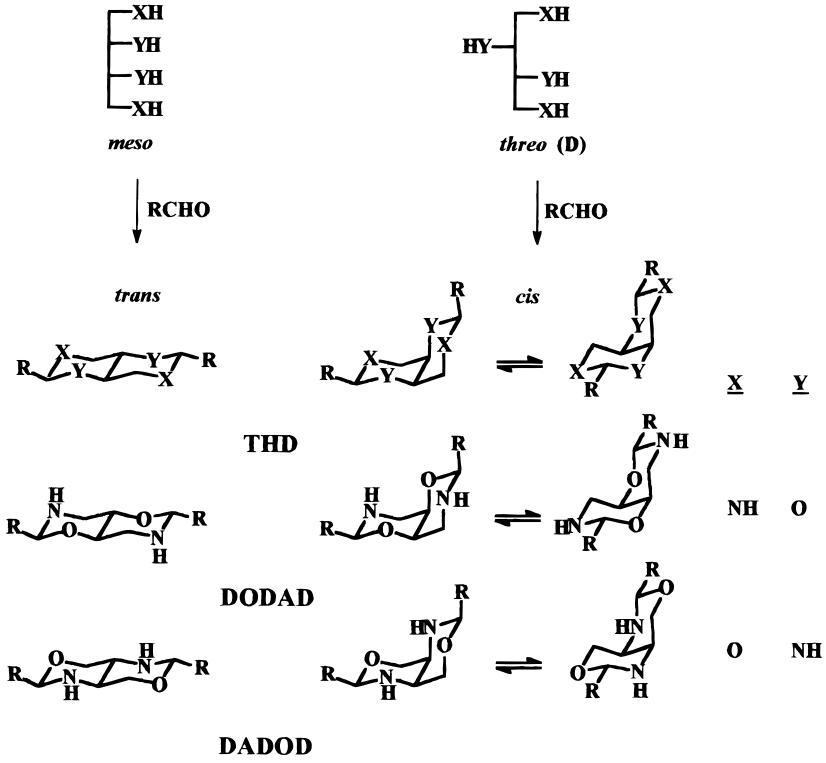
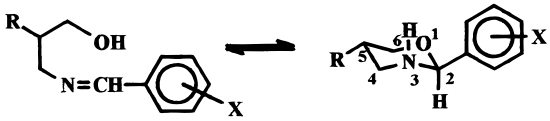
Scheme 1. Formation and Stereochemistry of 1,3,5,7-Tetraheterodecalin (THD), Especially 1,5-Dioxa-3,7-diazadecalin (DODAD) and 1,5-Diaza-3,7-dioxadecalin (DADOD)



Scheme 2. Ring−Chain Tautomerism in Tetrahydro-1,3-oxazanes



to probe the effect of electron-withdrawing (EW) and -donating (ED) groups: the reaction of *threo*-1,4-diamino-2,3-butanediol (**1***t*) with *p*-EW-substituted benzaldehydes (Scheme 3) in water provided the metastable Schiff bases (e.g., **3***t*), followed by (mainly) the DODAD products (e.g., **7***ci*), whereas *threo*-2,3-diamino-1,4-butanediol (**2***t*) gave directly the *cis*-DADOD analogues (e.g., **8***ci*). Reaction in water was successful only with electron deficient aldehydes (**a**−**c**); in the case of ED substituents (**d**−**f**), hydrolysis was significant and the cyclic products were all but absent. Ethanol, however, behaved consistently along the entire series and was the solvent of choice.

The four *meso* and *threo* 1,4-diamino-2,3-butanediols (**1***m*, **1***t*) and 2,3-diamino-1,4- butanediols (**2***m*, **2***t*)[4] were reacted with six different *p*-substituted benzaldehydes in ethanol at room temperature. In these reactions, a ring−chain tautomeric mixture containing 11 components could be envisaged (Schemes 3 and 4). We found, however, that ring closure to 1,3-oxazane (Scheme 3) was largely preferred and five-membered ring products (Scheme 4) were absent or minor (<10%) and were disregarded. The condensations took place in good to excellent yields; some of the products, especially in the *meso* series, crystallized from the reaction solution, while the others were isolated after evaporation and recrystallization. Pure products or their natural tautomeric mixtures were isolated this way and characterized in the solid and/or in solution.

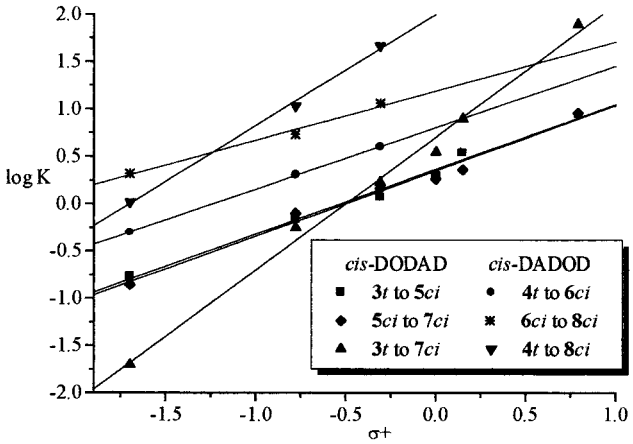


Figure 1. Linear regression analysis of the equilibrium data in the tautomeric mixtures of DODAD and DADOD in $CDCl_3$.

The allowed (*6-endo-trig*) first 1,3-oxazane ring closure of **3***t* may form in principle two 5,6-*cis* isomers and that of **3***m*, two 5,6-*trans* isomers (with axial/equatorial or diequatorial 5,6 substituents, respectively) on the corresponding 1,3-oxazane intermediates (**5**). As expected from conformational analytical tenets, all these intermediates (**5**) had equatorial 2-aryl and *N*-aral-6-aminomethylene groups, while the 5-hydroxyl occurred in *cis*-axial or *trans*-equatorial conformation, respectively. The second ring closure gave invariably the corresponding 2,6-diequatorially substituted *cis*- or *trans*-DODAD (**7***ci*, **7***tr*). As to the C=N double bond in **5**, both *Z* and *E* isomers coexist, with a preponderance of the latter.

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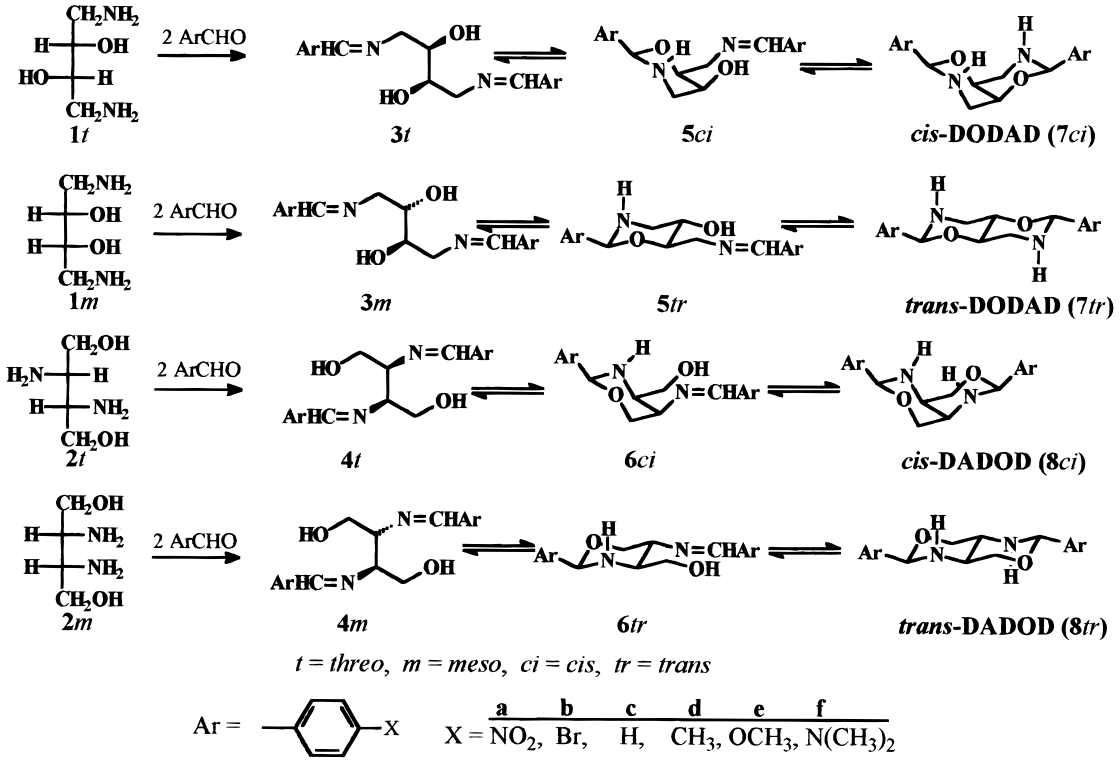
Scheme 3. Condensation Products of 1,4- and 2,3-Diaminobutanediols with Aromatic Aldehydes



Scheme 4. Possible Byproducts in the Ring-Closure Process of 3 and 4: Two Oxazolidine and Three Bi(5-oxazolidinyl) Diastereoisomers

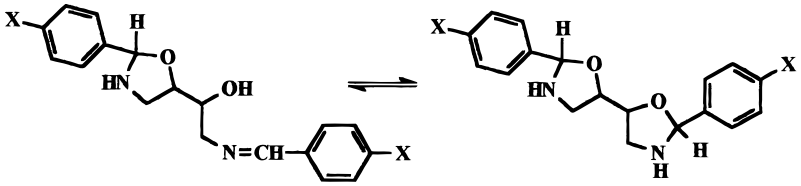


Table 1. Results of Linear Regression Analysis of Equilibria in the DODAD and DADOD Series: *Cis* Series in $CDCl_3$ (Figure 1) and *Trans* in DMSO-d_6 (Figure 2)

series	slope (ρ)	log K_0	c^b	r^c
3*t* to **5***ci*	0.68 ± 0.03	0.36 ± 0.03	0.51	0.995
5*ci* to **7***ci*	0.69 ± 0.04	0.35 ± 0.04	0.50	0.992
3*t* to **7***ci*	1.40 ± 0.06[d]	0.70 ± 0.05		0.996
4*t* to **6***ci*	0.65 ± 0.00[e]	0.80 ± 0.00	0.95	0.999
6*ci* to **8***ci*	0.52 ± 0.06[e]	1.19 ± 0.07	1.34	0.993
4*t* to **8***ci*	1.18 ± 0.07[d,e]	2.00 ± 0.07	-	0.998
3*m* to **5***tr*		0.09[f]	0.24	
5*tr* to **7***tr*		−0.78[f]	−0.63	
4*m* to **6***tr*		1.15[f]	1.30	
6*tr* to **8***tr*		−1.32[f]	−1.17	
3*m* to **5***tr*[g]	0.42 ± 0.02	−0.14 ± 0.02		0.994
4*m* to **6***tr*[g]	0.47 ± 0.01	0.33 ± 0.01		0.999

[a] Intercept. [b] *c* has been defined (by Fülöp et al.[5,6a]) as the sum of the steric and electronic effects of the substituents at positions 4, 5, and 6 in 1,3-oxazanes and expressed as the difference of intercepts for any substituted derivatives and the parent 2-phenyl-1,3-oxazane (−0.15): a positive *c*-value means better stabilization of the cyclic product with respect to the open chain precursor as compared to the phenyl-substituted system (and the other way around). [c] Correlation coefficient. [d] $\rho_1 + \rho_2 = 2\rho$. [e] Measurements reach scale limit. [f] Direct ratio measurements in $CDCl_3$ for **7***tr***c** and **8***tr***c** only ($\sigma^+ = 0$) (see text). [g] In DMSO-d_6.

The compounds in the *cis*-DODAD series (**7**) (Scheme 3) were soluble in chloroform and could be used for equilibrium analysis. Linear correlations with good correlation coefficients were indeed obtained, following the

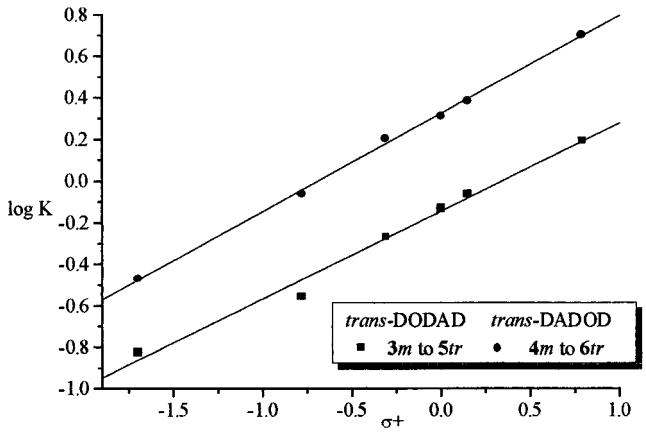


Figure 2. Linear regression analysis of the equilibrium data in the tautomeric mixtures of *trans*-DODAD and *trans*-DADOD in DMSO-d_6.

analysis of the tautomeric mixtures in terms of three major components: the double Schiff base (**3**), the 1,3-oxazane (**5**), and the final dioxadiazadecalin products (**7**). (Scheme 3). The presence of minor, five-membered ring byproducts (Scheme 4) should not affect the equilibrium under scrutiny, and they were disregarded. We analyzed the Hammett equations of the two processes **3** to **5** ($Z + E$) and **5** ($Z + E$) to **7** and, implicitly, **3** to **7** (Figure 1). To the best of our knowledge, the present paper describes

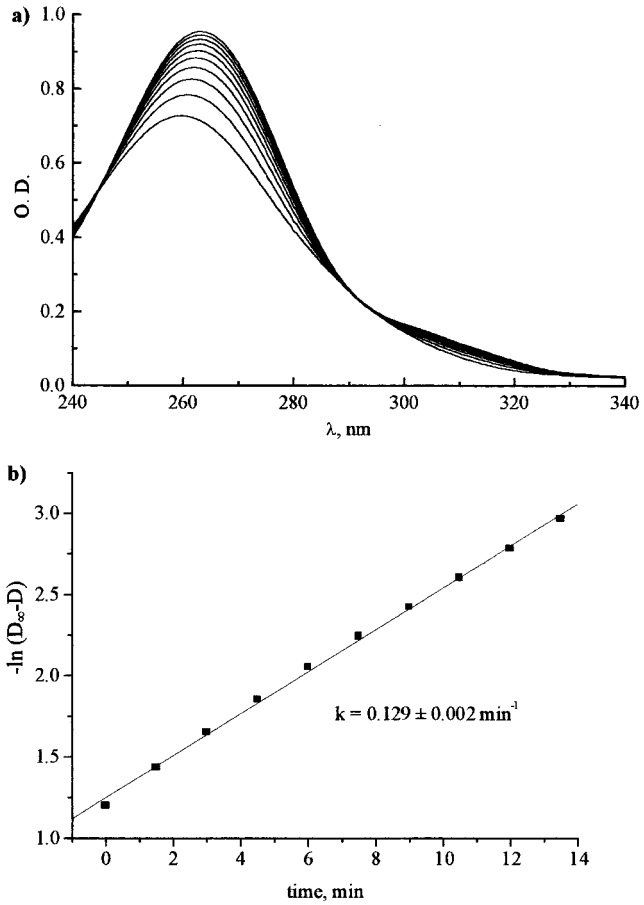


Figure 3. UV spectrophotometrically monitored reaction kinetics of the acid (TFA, 10^{-5} M) catalyzed ring closure of **3***ta* to **7***cia* at 28 °C.

the first example of such two-step ring−chain equilibria. In this *cis*-DODAD (**3**) series, the same ρ-value (0.69 ± 0.04) was found for both the first and the second ring closures (Table 1). This value is somewhat smaller than the standard oxazane value (0.76 ± 0.04);[5,6a] however, it is almost identical to the ρ-value which had been obtained for certain multicomponent tautomeric mixtures.[7a] The **7** to **3** ratio showed a very good linear correlation coefficient, and the slope was 1.40 ± 0.06, i.e., close to the theoretical 2ρ-value.

In all these cases, the ring−chain tautomeric ratio could be monitored by NMR, by integrating appropriate protons, *viz.*, azomethine protons (8 ppm) in **3** to **5** and 2-oxazane protons (5 ppm) in **5** to **7** (Tables 3, 5, 8, and 10—see Experimental Section and Supporting Information).

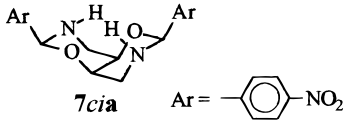
The *cis*-DADOD (**8**) series showed in $CDCl_3$ an extremely high ring/chain ratio, and open chain intermediates were detected only in the case of electron-donating groups (Scheme 3, **d**−**f**). This precluded a reliable linear analysis (Table 1) but sufficed for estimating the intercepts in this series (*vide infra*).

The *trans*-DODAD (**7***tr*) and *trans*-DADOD (**8***tr*) tautomeric mixtures (except those of **7***tr***c,d** and **8***tr***c,d**) were also not amenable to reliable analysis in chloroform, since the intermediates or end products exhibited poor solubility (precipitation of one of the components shifted the equilibrium arbitrarily). For this reason, a less reliable linear correlation was obtained, but **7***tr***c** and **8***tr***c** could be used for evaluation of the intercept—*c*-values (Table 1). Furthermore, we attempted a study of *trans*-DODAD and *trans*-DADOD compounds by ^{1}H NMR in DMSO-d_6 (Tables 12 and 13, see Supporting Information), but only the **3** to **5** and **4** to **6** ratios could be calculated. Linear correlations were observed (Figure 2), albeit with low accuracy, because of complete prevalence of the open-chain tautomers in DMSO solution and the measured ρ-values (0.42−0.47) were considerably lower than those in chloroform. The ^{1}H NMR data of the half-closed, monocyclic 1,3-oxazanes are displayed in two columns in Tables 13 and 14 (see Supporting Information) to stress the interesting fact that they are practically superimposed spectra of a Schiff base and 1,3-oxazane moiety.

Table 2. Observed (X-ray)[a] *vs* Calculated (MM3)[b] Selected Structural Parameters of 2,6-Di(*p*-nitrophenyl)-DODAD (7*cia*)

L (bond lengths, Å)	X-ray[c]	MM3[b]
O1−C2	1.424	1.419
O5−C6	1.425	1.419
O1−C9	1.438	1.424
O5−C10	1.425	1.424
C2−N3	1.425	1.456
C6−N7	1.447	1.456
N3−C4	1.472	1.461
N7−C8	1.474	1.461
C4−C10	1.517	1.525
C8−C9	1.501	1.525
C9−C10	1.527	1.521
T **(torsion angles, deg)**	**X-ray**	**MM3[b]**
O1−C2−N3−C4	57.6	65.8
O5−C6−N7−C8	58.5	65.8
O1−C9−C10−O5	71.9	68.2
N3−C4−C10−O5	−74.7	−70.4
N7−C8−C9−O1	−76.5	−70.4
O1−C2−C11−C12	13.3	−151.0
O5−C6−C20−C21	−177.8	−151.0

[a] Reference 4a and Cambridge Structural Database. [b] The MM3(92) force field[10] was used, including our modification for the *gauche effect* in O−C−C−O systems (MM3-GE).[2b] [c] esd's 0.006−0.008.



While the first ring closure in DODAD and DADOD systems behaves similarly in both the *cis* and *trans* series, the second ring closure is relatively preferred in the *cis* series of both systems. The following trend in the ease of the second cyclization, as compared to the first one, could be observed: *cis*-DADOD > *cis*-DODAD > *trans*-DODAD > *trans*-DADOD. The *cis*-bicyclic tautomers (**7***ci*, **8***ci*) are more stable ($c > 0$, see footnote b in Table 1) whereas the *trans*-fused bicyclic systems (**7***tr*, **8***tr*) are destabilized ($c < 0$) with respect to the reference 2-phenyltetrahydro-1,3-oxazanes.[5,6a]

This is in contrast to cyclohexane-fused oxazanes, for which *trans*-fused systems have better stability than the *cis*-fused ones.[5,7a] In both *trans* series the second cyclization steps appear to be handicapped by strain in the transition state, more than in the *cis* series. At the same time, the *cis* bicyclic products are stabilized by intramolecular hydrogen bonding, especially in *cis*-DADOD.[4] This peculiar NH- - -O bond is one of the reasons for the N−H axial conformations in most of the structurally defined DODAD and DADOD compounds at hand (the main reason being the *anomeric effect* in the N−C−O moieties, *vide infra*).

Table 3. ^{1}H NMR Data of 2,6-Diaryl-*cis*-DODAD (7*ci*, cf. Scheme 3) in $CDCl_3$/TMS (δ in ppm, Mult., *J in* hertz)

		H_2	H_4			H_9	Ar	
Ar	**7*ci***	δ	δ	^2J	^3J	δ	δ	^3J
p-nitrophenyl	**a**	5.38 s	3.44 dd	14.4	0.9	3.75 bs	8.20 d	8.8
		$^3J = 10^a$	3.31 d	14.4			7.74 d	8.8
p-bromophenyl	**b**	5.25 s	3.36 dd	14.3	0.8	3.66 bs	7.48 d	8.4
			3.24 d	14.3			7.40 d	8.4
phenyl	**c**	5.31 s	3.39 d	14.5		3.68 bs	7.38 m	
			3.26 d	14.5				
p-tolyl	**d**	5.27 s	3.36 d	14.5		3.65 bs	7.41 d	8.0
			3.24 d	14.5			7.17 d	8.0
p-anisyl	**e**	5.26 s	3.36 d	14.5		3.65 bs	7.45 d	8.5
			3.23 d	14.5			6.90 d	8.5
p-Me_2N-phenyl	**f**	5.22 s	overlapping signals					

[a] When taken immediately after extraction from basic aqueous solution, vicinal coupling of (axial) N−H with H_2 could be observed.

Table 4. ^{13}C NMR Data of 2,6-Diaryl-*cis*-DODAD (7*ci*, cf. Scheme 3) in $CDCl_3$/TMS (δ in ppm, Mult.)

		C_2	C_4	C_9	Ar
Ar	**7*ci***	δ (d)	(t)	(d)	δ
p-nitrophenyl	**a**	87.0	49.7	69.7	127.0, 123.4
p-bromophenyl	**b**	88.2	50.4	70.3	132.0, 128.4
phenyl	**c**	88.3	49.9	69.7	128.7, 128.4, 125.9
p-tolyl	**d**	88.9	50.5	70.3	126.4, 129.0
p-anisyl	**e**	88.7	50.5	70.3	129.1, 114.8
p-Me_2N-phenyl	**f**				

While *threo*-2,3-diamino-1,4-butanediol (**2***t*) reacted with *p*-EW-substituted benzaldehydes to give right away the corresponding *cis*-DADOD (**8***ci***)** products and we were not able to see any of the Schiff base intermediates, the time required by the metastable Schiff bases (*e.g.*, **3***t***a**) made from *threo*-1,4-diamino-2,3- butanediol (**1***t*) with *p*-EW-substituted benzaldehydes (Scheme 3), to undergo ring closure in chloroform solution, ranged from 1 to several weeks. In fact, the slow kinetics of these tautomeric mixtures made possible the isolation of the various components. The process could be, however, acid catalyzed (by trifluoroacetic acid), as shown by the ring closure of the double Schiff base (**3***t***a**) (λ_{max} 217 nm, ϵ 18 400; 284.5 nm, ϵ 30 800) or, rather, of its instantaneously protonated form (λ_{max} 259.5 nm) to *cis*-DODAD (**7***ci***a**) (λ_{max} 264 nm, ϵ 5500) in acetonitrile. This UV-monitored process (Figure 3a) proceeded with practically first-order kinetics ($k = 0.129$ min^{-1}, $t_{1/2}$ 5.3 min) (Figure 3b). This and the occurrence of three virtual isosbestic points (Figure 3a) imply that the monocyclic intermediate is very short-lived in these conditions.

We could observe an interesting expression of this behavior, namely, the spontaneous but slow (1 month) ring-closing process of **3***t***a** to **7***ci***a** *in the solid phase*. We found, however, a closely related precedent, *viz.*, 2-*p*-nitro-1-oxa-3-aza-*cis*-decalin, formed by ring closure of the corresponding Schiff base in the crystal, as found by CP/MAS ^{13}C NMR by Riddell et al.[7c]

Another interesting manifestation of this ring−chain tautomerism in the crystal was found while some relevant geometrical parameters were scrutinized (Table 2) in the reported[4a] X-ray diffraction structure of 2,6-di(*p*-nitrophenyl)-DODAD (**7***ci***a**), in particular, the bond lengths and torsion angles (the results of the analogous DADOD molecule, **8***ci***a,** were of relatively low precision[4a] and, hence, the geometrical data not good enough for discussion in this context). At the same time, we were interested in probing the MM3 force field[10] as a computational tool for these systems, especially for emulation of structural and conformational details; we used our

Table 5. ^{1}H NMR Data of 2,6-Diaryl-*cis*-DADOD (8*ci*, cf. Scheme 3) in $CDCl_3$/TMS (δ in ppm, Mult., *J* in hertz)

		H_2	H_4			H_9	Ar	
Ar	**8*ci***	δ	δ	^2J	^3J	δ	δ	^3J
p-nitrophenyl	**a**	5.32 s	4.26 d	11.8		3.12 bs	8.19 d	8.9
		$^3J = 13.2^a$	4.15 d	11.8		$^3J = 11^a$	7.72 d	8.9
p-bromophenyl	**b**	5.21 s	4.20 d	11.8		3.05 bs	7.49 d	8.6
			4.09 d	11.8			7.40 d	8.6
phenyl	**c**	5.27 s	4.23 d	11.8		3.08 bs	7.72 m	
			4.11 dd	11.8,	1.1		7.50 m	
p-tolyl	**d**	5.23 s	4.20 d	11.8		3.04 bs	7.40 d	8.0
			4.09 dd	11.8	1.5		7.16 d	8.0
p-anisyl	**e**	5.22 s	4.20 d	11.9		3.03 bs	7.43 d	8.6
			4.09 dd	11.9,	1.6		6.89 d	8.6
p-Me_2N-phenyl	**f**	5.19 s	4.25 d	11.8			7.36 d	8.7
			4.08 d	11.8			6.66 d	8.7

[a] When taken immediately after extraction from basic aqueous solution, vicinal coupling of (axial) N−H with H_2 and H_9 could be observed.

Table 6. ^{13}C NMR Data of 2,6-Diaryl-*cis*-DADOD (8*ci*, cf. Scheme 3) in $CDCl_3$/TMS (δ in ppm)

		C_2	C_4	C_9	Ar
Ar	**8*ci***	δ (d)	δ (t)	δ (d)	δ
p-nitrophenyl	**a**	87.0	71.3	49.6	127.0, 123.5, 147.9, 146.4
p-bromophenyl	**b**	88.2	71.9	50.2	132.1, 128.3
phenyl	**c**	88.9	72.0	50.3	129.1, 126.4
p-tolyl	**d**	88.8	71.9	50.1	126.2, 129.6
p-anisyl	**e**	88.7	71.9	50.2	127.5, 114.3, 132.9, 130.6
p-Me_2N-phenyl	**f**	89.0	71.9	50.2	130.6, 112.2

modification for the *gauche effect* in O−C−C−O-containing systems, MM3-GE.[2b]

While the MM3 calculated structures where inevitably C_2 symmetric (Table 2), the X-ray structure showed albeit gross conformational C_2 symmetry, but departure from it in certain geometrical details. The most remarkable discrepancy was that between C2−N3 and C6−N7. It can be easily interpreted as a consequence of the above ring−chain tautomerism, especially in the second stage of DODAD closure. One should, however, remember that we deal here with systems bearing, R−N−C−O−R′ units, which are prone to the known *anomeric effect*.[11,12] In fact, two unequal *anomeric effects* may operate in the appropriate conformation: a weak $lp_O-\sigma^*_{C-N}$ one, accompanying the strong, synergized $lp_N-\sigma^*_{C-O}$ anomeric

(10) MM3. QCPE (latest public version) or the official distributors are Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065, and Tripos Associates, 1699 S. Hanley Road, St. Louis, MO 63144. (b) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551 and subsequent articles.

(11) (a) Senderowitz, H.; Aped P.; Fuchs B. *Helv. Chim. Acta* **1990**, *73*, 2113. (b) Senderowitz, H.; Aped P.; Fuchs B. *J. Comput. Chem.* **1993**, *14*, 944.

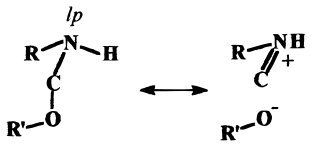
(12) Senderowitz, H.; Fuchs, B., *J. Mol. Struct. THEOCHEM* **1997**, *395/396*, 123.

Table 7. Physical and Analytical Data of Various *Cis* and *Trans* DODAD and DADOD Equilibrium Products and Mixtures[a]

compd	mp (°C)[b]	elemental analysis or HR-DCI-MS (*m/z*: MH^+)	
cis-DODAD series			
a	176 (dec)[b,c]	$C_{18}H_{18}N_4O_6$	C 55.94, H 4.70, N 14.51; found C 55.80, H 4.63, N 14.42
b	192[b,c]	$C_{18}H_{18}N_2O_2Br_2$	DCI-MS: 455.1
c	140[b,d]	$C_{18}H_{20}N_2O_2$	297.1603 obsd 297.1601
d	145[b,d]	$C_{20}H_{24}N_2O_2$	325.1916 obsd 325.1919
e	115[b,d]	$C_{20}H_{24}N_2O_4$	357.1814 obsd 357.1813
f	158[b,d]	$C_{22}H_{30}N_4O_2$	383.2447obsd 383.2447
cis-DADOD series			
a	170[b,d]	$C_{18}H_{18}N_4O_6$	C 55.96, H 4.70, N 14.50, found C 55.97, H 4.68, N 14.43
b	150[b,e]	$C_{18}H_{18}N_2O_2Br_2$	DCI-MS: 455.0
c		$C_{18}H_{20}N_2O_2$	297.1603 obsd 297.1603
d	105[b,f]	$C_{20}H_{24}N_2O_2$	325.1916 obsd 325.1916
e	122[b,f]	$C_{20}H_{24}N_2O_4$	357.1814 obsd 357.1822
f	155[b,d]	$C_{22}H_{30}N_4O_2$	383.2447 obsd 383.2447
trans-DODAD series			
a	215[b,d]	$C_{18}H_{18}N_4O_6$	387.1305 obsd 387.1306
b	186[b,d]	$C_{18}H_{18}N_2O_2Br_2$	DCI-MS: 455.1
c	144[b,e]	$C_{18}H_{20}N_2O_2$	297.1603 obsd 297.1602
d	148[b,e]	$C_{20}H_{24}N_2O_2$	325.1916 obsd 325.1912
e	161[b,c]	$C_{20}H_{24}N_2O_4$	357.1814 obsd 357.1811
f	199[b,c]	$C_{22}H_{30}N_4O_2$	383.2447 obsd 383.2451
trans-DADODseries			
a	178	$C_{18}H_{18}N_4O_6$	387.1305 obsd 387.1303
b	184	$C_{18}H_{18}N_2O_2Br_2$	DCI-MS: 455.1
c	116	$C_{18}H_{20}N_2O_2$	297.1603 obsd. 297.1600
d	153	$C_{20}H_{24}N_2O_2$	325.1916 obsd 325.1907
e	183[b,c]	$C_{20}H_{24}N_2O_4$	357.1814 obsd 357.1814
f	219[b,c]	$C_{22}H_{30}N_4O_2$	383.2447 obsd 383.2447

[a] The pure end products show the same properties, since on heating they attain rapidly the equilibrium composition. All physical data and analyses should be understood accordingly. [b] Recrystallized from *c,* EtOH; *d, i*PrOH; *e,* MePh; *f, t*-BuOMe.

interaction, due to the good lp donor (N) *anti* positioned to an excellent acceptor (O) (see below). Notably, the valence bond representation of this molecular orbital mixing, is a double bond−no bond resonance, the thermodynamic counterpart of which is the above-discussed ring−chain tautomerism.



This conformation demands an axially positioned hydrogen on N, as is indeed observed in the X-ray structure of **7***ci***a** (Table 2). In fact, this was proven by NOE and double irradiation experiments of **7***ci***a** in (acidless) solution as well (Table 3).

Conclusions

In conclusion, an LFER study of the ring−chain tautomeric reactions of *threo*- and *erythro*-1,4-diamino- and -2,3-diaminobutanediols (**1**, **2**) with six *p*-substituted benzaldehydes enabled us to understand them and to anticipate the outcome of such future processes. The end products are the novel *cis*- and *trans*-1,5-dioxa-3,7-diazadecalin (DODAD, **7***ci*, **7***tr*) and -1,5-diaza-3,7-dioxadecalin (DADOD, **8***ci*, **8***tr*) systems. The double 1,3-oxazane ring closures take place mostly *via* Schiff bases and are moderately polar ring−chain tautomeric reactions with low positive ρ-values (0.69), affected by solvent, steric strain, stereoelectronic effects, and intramolecular hydrogen bonds. These are relatively slow processes, which may occur in the solid as well but are greatly enhanced by acid catalysis. The insight gained is expected to be of considerable significance in the design of new ligands and complexes based on the DODAD and DADOD and the double Schiff base systems as well as of new potential anticancer and C_2 HIV protease inhibitor drugs.[9]

Experimental Section

General. Melting points were determined on a capillary melting point apparatus and are not corrected. Elemental analyses were performed at the Microanalytical Laboratory, Hebrew University, Jerusalem. Mass spectra were measured in DCI-MS and HR-MS mode. ^{1}H and ^{13}C NMR spectra were recorded on 200 or 500 MHz spectrometers and referenced to TMS. Conformational assignments were based on NOE experiments. UV spectra were measured on a UV spectrophotometer with kinetic attachments. Commercially available reagents and solvents were purified and dried when necessary by common methods.

Starting Materials. The starting diastereoisomeric diaminobutanediols (**1** and **2**) dihydrochlorides were prepared as described[4] and purified as follows.

threo-1,4-Diamino-2,3-butanediol dihydrochloride (**1***t*·2HCl) (600 mg) was dissolved in a methanol/water solution, passed through a strongly basic anion exchange column (Amberlist A-26, OH^- form), and eluted with methanol/water. Evaporation gave 346 mg of *threo*-1,4-diamino-2,3- butanediol (**1***t*) (93%). A similar procedure was used for *threo*-2,3-diamino-1,4-butanediol (**1***m*). The *meso* diaminobutanediols (**1***m* and **2***m*) were isolated as in the original procedures.[4]

General Reaction and Equilibrium Procedure. A total of 50 mg of the free base (*e.g.,* **1***t*) was dissolved in 10 mL of ethanol, and an appropriate aromatic aldehyde (2.2 molar equiv) was added. After standing overnight at room temperature, the crystalline product was collected from the ethanol solution; alternatively, the solvent was evaporated and the solid residue was washed of excess aldehyde and crystallized from a suitable solvent, usually *i*-PrOH (yields: 70−90%).

Each of these products was taken up in chloroform-*d* or DMSO-d_6 and left to reach constant composition at room temperature. All plotted correlation data were recorded on these equilibrium mixtures.

The resolved NMR spectral data of the DODAD and DADOD products are given in Tables 3−6 for clearer scrutiny of the like *vs* unlike, *i.e.*, coupling constants *vs* chemical shifts, respectively. Other relevant physical data of all isolated compounds or equilibrium mixtures are assembled in Table 7. The NMR spectral data of the Schiff bases and intermediate products are given in Tables 8−14, available as Supporting Information.

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Supporting Information Available: NMR spectral data of Schiff bases and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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