The 1,3,5,7-Tetraazadecalins: Structure, Conformation, and Stereoelectronics. Theory vs Experiment[1]

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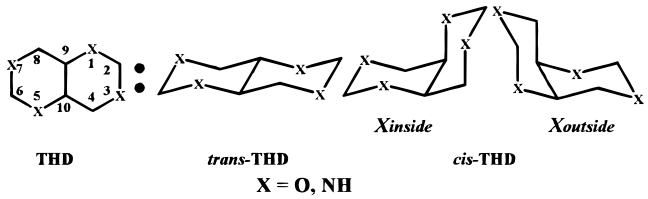
cis- and *trans*-1,3,5,7-tetraazadecalin (TAD) (**2** and **4**) and several *N*-Me (**7**−**9**) and *N*-acyl (**10**−**12**) substituted derivatives in the *cis* and *trans* series were prepared and characterized. The X-ray structures of **4** and **12** were analyzed and the conformational equilibria of **2** and **11** were evaluated by VT-NMR. A QM (ab initio) and MM computational study was carried out, to provide relative stabilities and geometrical parameters, which were compared with experiment. The MM2-AE (modified for the anomeric effect in N−C−N containing molecules) and MM3 force fields are useful tools for these systems. The results were interpreted in the light of stereoelectronic effects in such fused 1,3-diazane systems.

Introduction

We have recently been investigating the general type of 1,3,5,7-tetraheterodecalin (THD) systems (Scheme 1). Besides the basic interest in their rich stereoelectronic features, we conceived a general scheme for new host systems built on *cis*-THD (Xinside) core units, viz., podands and macrocycles bound to possess good ion or molecule complexation ability. These ideas have been implemented first in the diacetal, tetraoxadecalin (X = O) (TOD) series,[1a,2] establishing the validity of the approach to new host design. A compelling sequel was the investigation of the diaminal, 1,3,5,7-tetraazadecalin (TAD) series (X = NH). To start with and to back-up its anticipated and observed[1b] good complexation behavior, we sought insight in the steric and electronic features of the diastereomeric molecules.

Aminals are known by now as viable, reasonably stable, and usefully reactive systems.[3−5] The documented cases include imidazolidines[3,4] and diazanes,[3,5] and we had studied also the bicyclic 1,4,5,8-tetraazadecalins.[6] In the 1,3,5,7-tetraazadecalin (TAD) series, Willer et al. had prepared directly the tetra-*N*-nitroso- and tetra-*N*-nitro-1,3,5,7-TAD derivatives,[7] and very recently, some 2,6-dialkyl-substituted TAD compounds were reported.[8] The parent tetraazadecalins, however, have not been secured and defined, and the characteristics of the system have not been explored.

Scheme 1. 1,3,5,7-Tetraheterodecalin (THD) System



We describe now in detail[1b] the isolation and full characterization of *trans*- and *cis*-1,3,5,7- tetraazadecalin (TAD)[32] and of certain N-substituted derivatives of interest, including their stereoelectronic properties. The experimental efforts were accompanied by theoretical ones, namely, high level ab initio calculations, to scrutinize the geometrical features and relative stabilities of *trans*- and *cis*-TAD diastereomers and conformers and molecular mechanics as a practical and reliable tool for computation and modeling of large systems.

Results and Discussion

The reaction of (± or +)-*threo*- (**1**) or *erythro*-1,2,3,4-tetraaminobutane (**3**) (TAB)[7] with formaldehyde (Scheme 2) provided the parent *cis*- (**2**) and *trans*-1,3,5,7-tetraazadecalin (**4**) (TAD), respectively. The reactions are fully stereospecific, i.e., the *meso* character of *erythro*-TAB (**3**) is preserved in the centrosymmetric (*Ci*) *trans*-TAD (**4**), while the (C_2) dissymmetry of the *threo*-TAB (**1**) is preserved in the *cis*-TAD (**2**) product. Both diastereomeric products were obtained in high purity, and their

(1) New Supramolecular Host Systems. 9. (a) Part 8. Linden, A.; Rüchardt, Chr.; Beckhaus, H.-D.; Verevkin, S. P.; Ganguly, B.; Fuchs, B. *trans*- vs *cis*-1,3,5,7-Tetraoxadecalin: A Structural, Thermochemical and Computational Study. Submitted. (b) Part 7: Reany, O.; Goldberg, I.; Grabarnik, M.; Abramson, S.; Star, A.; Fuchs, B. *Tetrahedron Lett.* **1997**, *38*, 8073. This contains a short preliminary report of part of these results.

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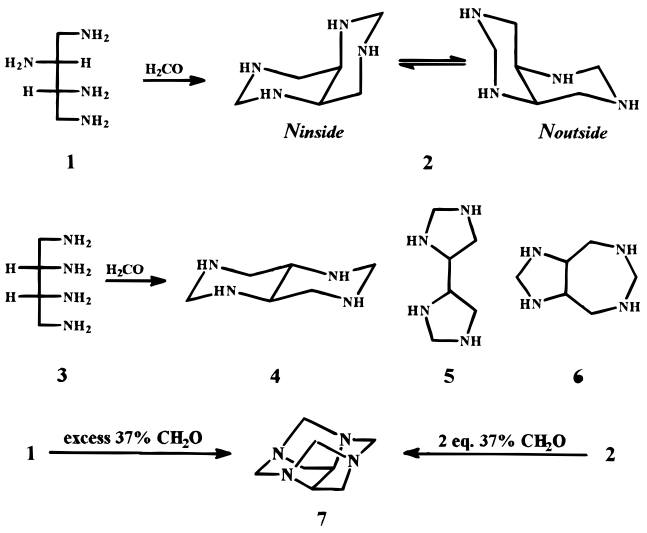
Scheme 2. Reactions of *threo*- (1) and *erythro*-1,2,3,4-Tetraaminobutane (3) with Formaldehyde



NMR spectra showed no evidence of the ring−chain tautomerism that has been reported for certain 1,3-diaza heterocycles.[9,10] FAB-MS analysis confirmed the molecular formulas, while NMR spectroscopy indicated that in our procedures only tetraazadecalins were formed and none of the possible isomeric (Scheme 2) bi(5-imidazolidinyl) (**5**) or 1,3-diazolano-1,3-diazepane (**6**) systems.[7] An additional, entirely new product was isolated in a variant of the synthetic procedure for *cis*-1,3,5,7-TAD, namely, using formaldehyde in excess with **1**, to give 1,7;3,5-dimethylene-*cis*-1,3,5,7-TAD (**7**). **7**, which is the smallest TAD cage, was obtained also by reacting *cis*-1,3,5,7-TAD (**2**) with 2 equiv of formaldehyde. This fact was taken as a further indication that the mode of formation of **7** is not one involving bridging of two imidazolidine rings in *threo*-**5**.

The ^{1}H NMR spectrum of the *cis* isomer **2** (in D_2O) exhibits only five signals, δ 3.88, 3.49, 2.93, 2.83, and 2.69, in a ratio of 1:1:1:1:1, endorsing the symmetrical structure. The δ 3.49 and 3.88 resonances are coupled, with $^2J = 12.9$ Hz, allowing their assignment to the C2,6 equatorial and axial protons, respectively. The double doublet at δ 2.93 was assigned, based on NOE and the large geminal coupling ($J_{gem} = -14.2$ Hz), to the C4,8 axial protons and the broad doublet at δ 2.83 to the equatorial ones. The broad singlet at δ 2.69 was readily assigned to the angular C9,10 protons. The small vicinal coupling constants at δ 2.93 and 2.83 indicate that both H4,8 protons are in a *gauche* relationship to the adjacent methine proton. The ^{13}C NMR spectrum also revealed the symmetry of the molecule, with only three carbon signals, all of which could be assigned unambiguously on the basis of chemical shifts and DEPT experiments, viz., δ 61.9 (C2,6), 51.6 (C9,10), and 50.6 (C4,8).

While the *trans* isomer (**4**) (vide infra) is fixed, the *cis*-fused isomer (**2**) undergoes conformational ring inversion between the Ninside and Noutside forms (Scheme 2). To evaluate the $\mathbf{2}_{Ninside} \rightleftharpoons \mathbf{2}_{Noutside}$ equilibrium in solution, we carried out a variable temperature VT-NMR study of **2** in D_2O, in the range 299−344 K, focusing on $^3J_{4,10}$: (i) $^3J_{Nin} = {}^3J_{4ax,10}$ in $\mathbf{2}_{Ninside}$ and (ii) $^3J_{Nout} = {}^3J_{4eq,10}$ in $\mathbf{2}_{Noutside}$. A typical $^3J_{4ax,10}$ value (1.9 Hz), which we used for $^3J_{Nin}$, was chosen from conformationally stable 2,6-diequatorially substituted derivatives of **2** in our hands, e.g., 2,6-diaryl-*cis*-1,3,5,7-TAD compounds[1b] and the $^3J_{4eq,10}$ value for J_{Nout} was taken from the ^{1}H NMR analysis of 1,3,5,7-tetraacetyl-TAD (4.5 Hz) (vide infra). Using the well-known relationships $J_{obs} = XJ_{Nin} + (1 + X)J_{Nout}$ and $\Delta G° = -RT \ln K = \Delta H° - T\Delta S°$, one comes up with $\Delta H° = 6.3 \pm 1.3$ kcal mol^{-1}, $\Delta S° = 17 \pm 6$ cal (mol K)$^{-1}$, and a free energy difference of $\Delta G° = 1.0 \pm 3.0$ kcal mol^{-1}. Direct evaluation from the measurement at 299 K gave $\Delta G° = 1.0$ kcal mol^{-1} ($K_{299} = 0.18$, i.e., 85% $\mathbf{2}_{Ninside}$), in excellent agreement with the above value. The high value obtained for the entropy difference may be attributed to a strong (polar) solvent effect, viz., among the two isomers, $\mathbf{2}_{Noutside}$ assembles a more disordered solvating sphere of water molecules.

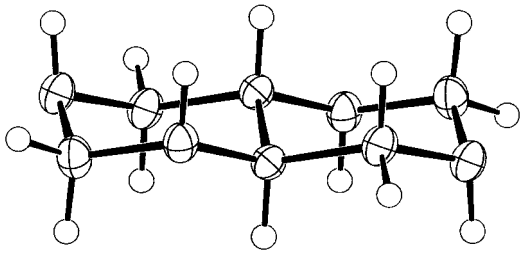


Figure 1. ORTEP drawing from the X-ray analysis of *trans*-1,3,5,7-TAD (**4**) with 50% probability ellipsoids of the non-hydrogen atoms.

The *trans* isomer (**4**) exhibited only four ^{1}H NMR signals, δ 3.84, 3.46, 2.95, and 2.42, in a ratio of 1:1:1:2, confirming its high symmetry. The δ 3.46 and 3.84 doublets ($^2J = 12.7$ Hz) were assigned to the C2,6 equatorial and axial protons, respectively. The remaining signals were complex, but NOE experiments made possible the assignment for H4,8$_{eq}$ (2.95), H9,10 (2.42), and H4,8$_{ax}$ (2.42). In ^{13}C NMR only three signals, δ 62.6, 60.4, and 50.3, were assigned to C2,6, C9,10, and C4,8, respectively. C9,10 in *trans*-TAD resonate considerably downfield compared to those of the *cis* isomer, this being the most noticeable difference in the NMR chemical shifts between the *trans* and *cis* diastereomers. The increased shielding of C9,10 in the *cis* isomer (similar to that observed in the related *cis*-tetraoxadecalins[2]) is attributed to the internal gauche N−C−C−N moiety in its predominant Ninside form, compared to an *anti* arrangement in the *trans* isomer (vide infra).

The structure of *trans*-TAD (**4**) could be fully substantiated by a single-crystal X-ray diffraction analysis, albeit as a tetrahydrate. Figure 1 presents (a) an ORTEP drawing of **4** and (b) its crystal packing details, showing its centrosymmetric structure with (the first reported 1,3-diazane having) all axial N−H bonds. The geometric parameters of **4** are given in Table 1 and compared with those calculated by QM ab initio and MM methods (vide infra).

The TAD system (in any double chair configuration) has built-in C−N−C−N−C moieties in each of the two rings, in a g^+g^- arrangement. This implies a double *anomeric efect*[11] in each moiety, provided the N−H bonds

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Table 1. Calculated (QM ab Initio and MM) vs Experimental (X-ray) Parameters of *trans*-TAD (4) (*ax,ax,ax,ax*) Bond Lengths (*L*, Å), Bond Angles (*A*, deg), and Torsion Angles (*T*, deg)

	X-ray	*ab initio*	MM2-AE	MM3
		L		
N1−C2	1.474(2)	1.467	1.462	1.466
C2−N3	1.465(2)	1.462	1.461	1.465
N1−C9	1.471(2)	1.464	1.464	1.466
N3−C4	1.469(2)	1.467	1.463	1.465
C4−C10	1.522(2)	1.526	1.535	1.528
C9−C10	1.533(2)	1.534	1.539	1.529
		A		
C2−N1−C9	110.1(1)	110.4	109.6	110.5
C2−N3−C4	111.6(1)	111.9	109.8	111.1
N1−C2−N3	115.2(1)	116.8	116.9	112.9
N3−C4−C10	112.2(1)	112.4	109.8	110.8
N1−C9−C8	111.9(1)	112.0	110.8	111.7
N1−C9−C10	111.4(1)	112.6	109.4	109.2
C4−C10−C9	109.8(1)	109.7	110.6	109.7
		T		
C2−N1−C9−C8	−178.6(1)	−177.2	−177.1	−179.9
C2−N1−C9−C10	−55.2(1)	−52.9	−55.0	−58.6
N3−C2−N1−C9	54.8(1)	51.8	56.3	58.8
C2−N3−C4−C10	51.9(1)	50.6	53.9	54.3
N1−C2−N3−C4	−53.1(1)	−50.9	−55.7	−56.3
N3−C4−C10−N5	−177.7(1)	−178.6	−178.6	−176.7
N3−C4−C10−C9	−53.5(1)	−52.8	−57.3	−55.5
N1−C9−C10−C4	55.5(1)	54.5	57.8	57.4
N1−C9−C10−N5	180.0(1)	180.0	179.9	180.0
C4−C10−C9−C8	180.0(1)	180.0	180.0	180.0

are axial. To put this in perspective, one should recall that we had studied the generic R−X−C−Y−R (X = O, N, S; Y = O, NR, F) systems, including the RHN−C−NHR molecules, in the context of the anomeric effect.[12] The latter is defined as the tendency to assume a *gauche* rather than *anti* orientation arround the X−C and C−Y bonds (Scheme 3a). The currently most accepted explanation of the anomeric effect is, in MO terms,[11d] the delocalization of a X_π lone pair into the adjacent σ^*_{C-Y} orbital. Hence, this two-electron two-orbital stabilizing interaction implies an antiperiplanar *lp*-X−C−YR orientation in the above *gauche* conformation. In terms of valence bond theory,[11d,e] one may invoke the equivalent notion of double-bond−no bond resonance: *lp*-X−C−YR ↔ X^+=C $^-$YR or negative hyperconjugation. The anomeric effect is manifest in (1) structural parameters, e.g., shorter anomeric bonds at the donor X−C and longer ones at the acceptor C−Y and wider anomeric bond angles; (2) relative energy, i.e., greater stability of *gauche* (axial) forms over *anti* (equatorial) ones; and (3) stereoselective reactivity, i.e., variation of rates of attack at or around the anomeric center, all those as a function of torsion angles in R−X−C−Y−R′. In symmetrical R−X−C−Y−R moieties with X = Y, e.g., C−O−C−O−C, four conformations have to be considered: *aa*, ag^+, g^+g^+, and g^+g^- (Scheme 3a). This number increases for every additional substituent (e.g., Y = NHR), and therefore, we had to modify the definitions of the conformations in N−C−N units by referring to *lp*-N−C−N-*lp* (Scheme 3b).[12]

In the theoretical part of our study we aimed at understanding the steric and electronic interplay in this diastereo- and conformationally isomeric TAD manifold, by using high-level ab initio methods, along with establishing the availability of a reliable force field for reproducing properties (energies and geometries) of known TAD compunds and predicting those of new, related and desired systems.

Computational Methodology and Results

For the QM ab initio calculations we used a reasonably high basis set with electron correlation correction, which we had used with good success for stereoelectronic effects in related oxygen-containing systems.[13] The various conformers of each species were fully optimized at the MP2/6-31+G* level using the Gaussian 94[14] programs. These calculations were carried out on Cray J932 and IBM SP-2 supercomputers, which made possible computational jobs of this size. The conformers were defined as true minima by diagonalizing their Hessian (force constant) matrices at the same level and making sure that all vibrational frequencies are real. As to molecular mechanics, we applied both the MM3-92 and the MM2-AE force fields; MM2-AE is our reparametrized version of MMP2-87 for the anomeric effect in N−C−N moieties[12] (both MM2[15] and MM3[16] had not been initially parametrized for stereoelectronic effects in NCN). The results are displayed in Tables 1−3.

The C−N−C−N−C moieties in TAD were well modeled by *N,N′*-dimethylmethylenediamine (DMD),[12] with its lp_N-$\sigma^*_{C-N'}$ anomeric interactions (Scheme 3b). These contribute to the stabilization of both *lp*-N−C−N-*lp aa* (2 anomeric effects) and *ag* (1 anomeric effect) conformers relative to g^+g^+ and g^+g^- ones and the geometric features are affected as elaborated above, viz., an N−C−N-*lp* antiperiplanar orientation results in shortening of C−N(*lp*), elongation of C−N, and opening of N−C−N and C−N−C bond angles. MM2-AE accounted well for these stereoelectronic manifestations in DMD and other N−C−N-containing systems.[12]

We calculated *cis*-1,3,5,7-TAD (Ninside) in all its N−H conformations and the *trans* isomer in the most stable forms, including the all-axial form found in the X-ray analysis (Table 1). The calculated relative energies are shown in Table 2, and the geometric parameters of the most stable *cis*-1,3,5,7-TAD conformers are shown in

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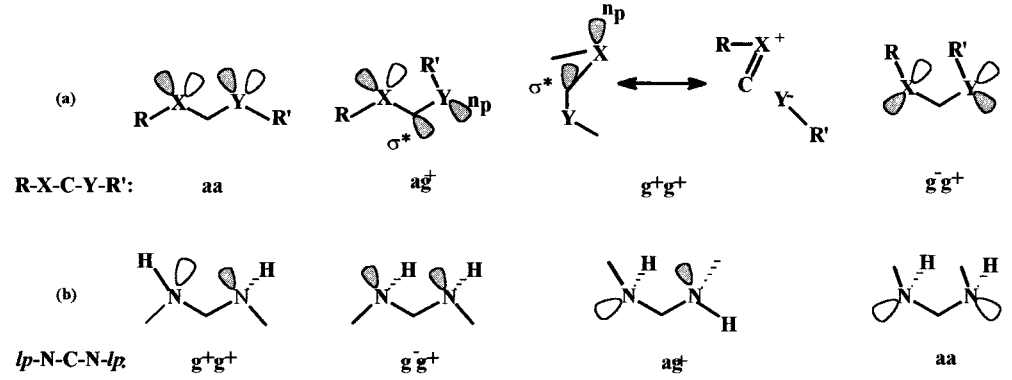
Scheme 3. Anomeric Effect in the General R−X−C−Y−R′ Case and in RHN−C−NHR Units

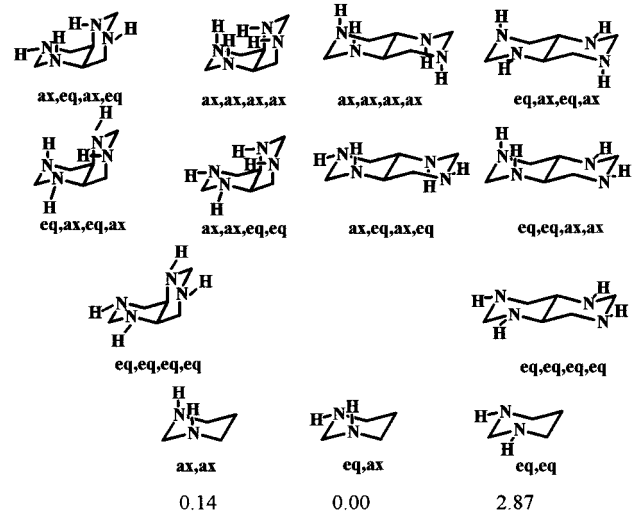


DMD

Table 2. Relative Energies (kcal mol^{-1}) of *trans*- and *cis*-1,3,5,7-TAD Conformers, from QM ab Initio and MM Calculations; Cf. Selected Forms Below, Including the Basic 1,3-Diazanes and Their Calculated Relative Energies[a]

N−H conformations				*cis*-TAD (**2**)			*trans*-TAD (**4**)		
1	3	5	7	ab initio[a]	MM2-AE	MM3	ab initio[a]	MM2-AE	MM3
eq	eq	eq	eq	(13.55)	12.31	4.55	6.08	10.08	0.43
eq	ax	eq	eq		5.32	0.76		7.12	0.49
ax	eq	eq	eq		6.75	2.31		7.02	0.25
eq	ax	eq	ax	2.43 (1.64)	1.55	0.52	0.00	3.83	0.00
ax	eq	ax	eq	0.00 (0.00)	0.82	0.00	0.30	3.78	0.24
eq	eq	ax	ax	1.82 (0.92)	2.90	0.35		5.67	1.87
eq	ax	ax	eq		1.86	1.10	0.09	3.70	0.06
ax	ax	eq	ax		0.00	1.30		2.11	1.33
ax	ax	ax	eq		0.40	1.98		1.95	1.35
ax	ax	ax	ax	3.01 (3.11)	0.52	4.31	0.04	0.00	2.35

[a] Calculated at MP2/6-31+G* level (cf. HF/6-31+G* values in parantheses).



Tables 1 and 3. The *ax,eq,ax,eq* is the most stable form in the *cis* series and the two equienergetic, *eq,ax,eq,ax* and *ax,ax,ax,ax*, forms are the most stable ones in the *trans* series (with other two following close behind). The geometric parameters follow the stated trends, as seen (best in the N−C−N bond lengths) in Tables 1 and 3. It appears that MM3 matches best the ab initio results (except for the high-energy forms).

It should be said at this point that the Noutside manifold is not included in the tables and in the discussion, for the sake of brevity and clarity; we have checked, of course, the Ninside vs Noutside relative stabilities (at the HF/6-31+G* level) and found big differences in favor of the former. Thus, for example, the most stable form in the Noutside series is also the *ax,eq,ax,eq* one, but is 4.4 kcal/mol higher than its Ninside counterpart.

Table 3. Calculated (QM ab Initio[a] and MM) *cis*-TAD (2) Most Stable Conformations[b] (see Table 2): Bond Lengths (*L*, Å), Bond Angles (*A*, deg), and Torsion Angles (*T*, deg)

	cis-TAD (**2**) (*ax,eq,ax,eq*)			*cis*-TAD (**2**) (*eq,ax,eq,ax*)		
	ab-initio	MM2-AE	MM3	*ab-initio*	MM2-AE	MM3
			L			
N1−C2	1.449	1.453	1.461	1.470	1.468	1.463
C2−N3	1.470	1.467	1.462	1.450	1.454	1.461
N1−C9	1.466	1.474	1.467	1.466	1.471	1.470
N3−C4	1.467	1.467	1.464	1.463	1.469	1.462
C4−C10	1.526	1.536	1.529	1.530	1.534	1.530
C9−C10	1.546	1.540	1.534	1.538	1.537	1.534
			A			
C2−N1−C9	112.1	110.2	110.5	112.1	111.1	111.9
C2−N3−C4	109.9	111.5	112.0	110.0	110.6	109.7
N1−C2−N3	111.6	113.0	111.6	111.6	112.7	111.4
N3−C4−C10	109.1	109.7	110.9	112.9	109.5	111.5
N1−C9−C8	109.7	109.1	108.8	109.0	108.9	109.1
N1−C9−C10	112.9	109.4	110.5	110.0	109.9	109.7
C4−C10−C9	109.9	110.3	110.6	110.0	110.8	110.1
			T			
C2−N1−C9−C8	171.0	176.2	176.1	176.4	176.0	176.5
C2−N1−C9−C10	48.9	55.4	54.5	55.7	54.5	55.8
N3−C2−N1−C9	−55.1	−58.5	−59.3	−60.7	−58.6	−60.5
C2−N3−C4−C10	−63.6	−57.2	−57.2	−55.8	−57.6	−57.5
N1−C2−N3−C4	63.7	59.2	60.1	59.1	60.1	60.3
N3−C4−C10−N5	−67.8	−64.0	−68.3	−68.8	−65.7	−66.4
N3−C4−C10−C9	56.4	56.3	53.2	51.9	55.3	54.1
N1−C9−C10−C4	−49.9	−54.8	−51.3	−50.8	−53.8	−52.1
N1−C9−C10−N5	71.7	65.3	69.2	69.2	66.5	68.0
C4−C10−C9−C8	−171.5	−174.8	−171.8	−170.8	−174.2	−172.2

[a] Calculated at MMP2/6-31+G* level. [b] The conformational notations refer to the N−H bond orientation at the nitrogen centers (see Table 2).

The occurrence of 1,3-diazane in a preferred diaxial (N−H) form had been inferred from NMR studies[5,17] but has received theoretical endorsement only in our previous MO studies ab initio.[12] Since it serves as a good model for the TAD case, we have recalculated it now at the augmented level (cf. Table 2, bottom). The *ax,ax* form is only very slightly of higher energy than the *eq,ax* one, and the *eq,eq* form is well (2.8 kcal/mol) above both. This is in line with our earlier[12] conclusions that the anomeric effect operates in N−C−N systems but is small (nearly

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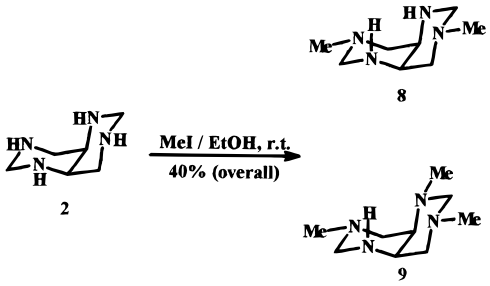
Scheme 4. Methylation Products of *cis*-1,3,5,7-Tetraazadecalin



1 kcal/mol), due the combination of a good *lp* donor but a bad σ^* acceptor, and steric effects (like two axial N−H bonds on moieties with short N−C bonds) counterbalance it effectively.

It appears that the anomeric effect in TAD stabilizes indeed the *aa* (2 anomeric interactions) and *ag* (1 anomeric interaction) in the C−N−C−N−C fragments, relative to g^+g^+ and g^+g^-. However, other steric and hydrogen bond type interactions are also contributing to the $ag > aa \gg g^+g^+$ order of relative stabilities found in the *cis*-TAD conformational manifold. These trends are well observed in Table 2 and the geometric manifestations in Table 3. Most interesting is that, according to the above results, *cis*-TAD with axial N−H bonds in positions 1 and 5 is energetically favored over that with axial N−H bonds in positions 3 and 7. This means that the anomeric effect in these moieties imparts increased nucleophilicity to N3 and N7. This should be corroborated by the reactivity of the nitrogen centers in alkylation reactions, as indeed found (vide infra).

***N*-Substituted TAD Compounds.** A series of *N*-substituted 1,3,5,7-*cis*-TAD derivatives was prepared and studied, to probe the relative reactivity of the nitrogen centers and for use in the planning of new macrocyclic receptor systems. Thus, the reaction of *cis*-1,3,5,7-TAD (**2**) and methyl iodide or bromide in excess provided 3,7-dimethyl- and 1,3,7-trimethyl-*cis*-1,3,5,7-tetraoxadecalin, DMTAD (**8**) and TMTAD (**9**), respectively (Scheme 4), but neither the mono- nor the tetramethyl derivative was observed. Attempts of stepwise methylation of *cis*-TAD by reductive alkylation with formaldehyde and formic acid (the Clarke−Eschweiler method)[18] were unsuccessful altogether.

The structural and conformation assignment of DMTAD (**8**) and TMTAD (**9**) were made by comparison with **2** and **7** and on the strength of ^{1}H NMR spectral analysis (Tables 4 and 5), by using two major criteria: Δea[5,19] and the geminal coupling constant (^2J) in the α-CH_2 group to the heteroatoms.[20−22] The Δea criterion is based on mixing of the antiperiplanar Nl_p electrons into the neighboring σ^*_{C-Hax} orbital, which imparts higher electron density to and increased shielding of that proton (Scheme 5).

Thus as shown[19b,22] in *N*,*N*-dialkylhexahydropyrimidines with both *N*-alkyl groups in the equatorial position, the chemical shift difference of N−CH_2−N protons (Δea) was higher than 1 ppm, whereas for only one equatorial alkyl group, Δea appeared to be moderate (0.5 ppm).

From this and the results obtained for 1,7:3,5-dimethylene-*cis*-1,3,5,7-TAD (**7**), in which both methylene groups are inevitably axial and the chemical shift differences for N−CH_2−N protons are very small (0.08 ppm), we could establish that all *N*-methyl groups in positions 1, 3, and 7 of compound **9** are equatorial (Scheme 4). The large Δea in this 2,6-CH_2 positions (1.29 and 0.84 ppm) can only be explained by an increase in electron density at the H(ax)-2,6 due to the axial *lp* on the adjacent N-1,3,7 and thus the methyl groups are bound to be equatorial. This can also be said for **8**, due to its large Δea in its 2,6-CH_2 positions (0.85 ppm).

As to the geminal coupling constants in a X−CH_2−Y arrangement, the inductive effect is independent of rotation about the carbon−heteroatom bond, but the hyperconjugation (back-donation) process depends on the degree of overlap and consequently on the dihedral angle between the lone pair electrons and the adjacent CH_2 bonds. Hence, J_{gem} is similarly affected, which makes it important in conformational analysis of (especially six-membered ring) heterocyclic systems. J_{gem} was estimated[21] to increase by about 1.8 Hz each time one of the orbitals of the geminal C−H bonds involved is antiparallel to a vicinal p-orbital of the free electrons of oxygen or nitrogen.[21,22] This effect is roughly additive[21] in OCH_2O of 1,3-dioxane systems, as well as in a large number of heterocyclic compounds containing NCH_2N and NCH_2X (where X = O, S) units.[22] Some of these results are included in Scheme 6 for comparison.

The large geminal coupling constant generated by 1,7:3,5-dimethylene-1,3,5,7-TAD (**7**) (Table 5) revealed that the lone pair on each of the four nitrogens bisects the H−H internuclear axis of the methylene groups in positions 2 and 6. The effect of changing the orientation of the N lone pair from bisecting the H−C−H angle to an antiperiplanar position is to reduce J_{gem} by 1.7−3 Hz. Indeed, in our compounds **2**, **8**, and **9**, a reduction of 1.1−3.5 Hz was observed in the geminal coupling constants of the NCH_2N methylene protons, in good agreement with previous results on 1,3-diazane derivatives.[5] The small value of J_{gem} in the NCH_2N unit in compound **9** suggests that both N lone pair and C−H bonds are antiperiplanar. This eclipsing effect causes a double hyperconjugation and, hence, a considerable change of J_{gem} (from −14 to −8 Hz).

Turning to *N*-acyl-substituted derivatives, we were interested to see how the conformations of these systems are affected by imparting the nitrogen partial trigonal character. Thus, the reaction of **2** and acetic anhydride or ethyl chloroformate led to one tetraacylated product in each case, i.e., 1,3,5,7-tetraacetyl-*cis*-1,3,5,7-tetraazadecalin (TATAD, **10**) and 1,3,5,7-tetraethoxycarbonyl-*cis*-1,3,5,7-tetraazadecalin (TECTAD, **11**) (Scheme 7).

The ^{1}H NMR spectra of **10** and **11** (Table 6) are entirely different from those of *cis*-TAD (**2**) and its N-alkylated

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Table 4. ^{1}H and ^{13}C NMR Data of 3,7-Dimethyl-*cis*-1,3,5,7-tetraazadecalin (8), 1,3,7-Trimethyl-*cis*-TAD (9), and 1,7:3,5-Dimethylene-*cis*-TAD (7) (200/50.3 MHz, $CDCl_3$, δ ppm, J Hz)

		2,6			4,8		9,10
		eq	ax	1,7- and 3,5-bridges	eq	ax	
7	^{1}H	4.39 (d) $^2J = 14.1$	4.28 (d) $^2J = 14.1$	4.28 (dd) $^2J = 9.8$ $^4J = 1.9$ 4.04 (d) $^2J = 9.8$	3.22 (dd) $^2J = 10.7$ $^4J = 1.9$	3.12 (dd) $^2J = 10.7$ $^3J = 4.6$	3.08 (bd) $^3J = 4.6$
	^{13}C	74.8		73.6	59.1		56.2
8	^{1}H	3.76 (dd) $^2J = 11.1$ $^4J = 1.8$	2.91 (d) $^2J = 11.1$		2.89 (dd) $^2J = 11.6$ $^4J = 1.8$	2.22 (dd) $^2J = 11.6$ $^3J = 1.8$	2.67 (t) $J = 1.8$
9	^{1}H	H-2 3.61 (d) $^2J = 7.6$ H-6 3.90 (d) $^2J = 11.0$	H-2 2.32 (d) $^2J = 7.6$ H-6 3.06 (d) $^2J = 11.0$		H-4 2.88 (m) H-8 3.25 (t) $^2J = 12.3$	H-4 2.08 (dd) $^2J = 11.6$ $^3J = 2.5$ H-8 2.24 (t) $^2J = 12.3$	H-10 2.73 (bs) H-9 2.49 (bs)
	^{13}C	79.9 (C-2); 70.5 (C-6)			55.5 (C-4); 59.4 (C-8)		52.5 (C_{10}) 59.4 (C_9)

Table 5. Various Chemical Shift Differences (δeq − δax = Δea) and J_{gem} Values of *cis*-TAD and Its N-Substituted Derivatives

	2 (**6**)		**4** (**8**)	
	$\Delta\delta$eq−ax	J_{gem}	$\Delta\delta$eq−ax	J_{gem}
	a. In $CDCl_3$ ($\Delta\delta$ ppm, J Hz)			
7	0.11	−14.1	0.1	−10.7
8	0.84	−11.1	0.67	−11.6
9	1.29	−7.6	0.8	−11.6
	0.84	−11.0	1.01	−12.3
	b. In D_2O ($\Delta\delta$ ppm, J Hz)			
2	0.39	−12.9	0.1	−14.2
4	0.38	−12.7	0.35	
7	0.11	−14.2	0.35	−12.1

derivatives **7**, **8**, and **9**. The observed vicinal coupling constants of the methylene protons in positions 4,8 are much larger than those expected from *cis*-TAD derivatives. Thus, $^3J_{4,8ax-ang} = 13.9-13.3$ Hz and $^3J_{4,8eq-ang} = 4.0-3.2$ Hz indicate that **10** and **11** are in Noutside form. This conformational behavior can be understood by invocation of the ring and pseudoallylic strain ($A^{1,3}$ strain)[23] caused by the four trigonal nitrogens in the Ninside form, in which the carbonyl oxygens lie in the plane of the rings. The ring flattening reduces the energy difference between the Ninside and the Noutside forms, and the latter, with the less hindered *N*-acyl groups, becomes favored. Three hindered rate processes are possible in **10** and **11**: (i) very fast nitrogen inversion,[24] (ii) ring inversion, and (iii) hindered rotation about N−COR. The latter is well-known[25] in R_2N-COX systems (X = alkyl, aryl, halide, or alkoxy) with energy barriers up to 25 kcal mol^{-1}. Several examples[25a] of hindered rotation of such systems with X = OR exhibit energy barriers of 13−16 kcal mol^{-1}. Ring inversion processes in trigonal atom-containing rings are bound to exhibit lower energy barriers.[26]

Theoretically, 10 rotamers are possible in **10** and **11**, as listed in Table 6 (bottom; degenerate forms were not included). Their expected ^{1}H NMR chemical shift patterns are given in Table 7. The temperature dependent ^{1}H NMR spectra of **10** and **11** at 223, 297, and 333 K are depicted, along with the detailed low-field aminal proton of **11**, in the Supporting Information.

The ^{1}H NMR spectrum of **10** shows several interesting features (Table 6 and Supporting Information). There are three sets of broadened signals attributed to three different tetracetylated isomers, with a population ratio of 66:24:10 determined from relative peak areas. Assignments of sets of signals of each isomer have been carried out following double irradiation experiments, but due to overlapping peaks or broad signals, only two of them (isomers **A** and **D**) are clearly resolved. In each set, the spectrum shows high chemical shift differences (Δea) between equatorial and axial protons in positions 2,6 and 4,8, as expected from deshielding effects of the carbonyl groups. The Δea of each isomer, in both 2,6 and 4,8 positions, are almost identical, viz., Δea(H2,6) = 2.17 ppm in **10D** vs 2.22 ppm in **10A** and Δea(H4,8) = 1.26 ppm vs 1.34 ppm, respectively. The geminal coupling constant of the aminal protons are similar in all isomers, i.e., $^2J = 13.3$ Hz. All these observations strongly implied that the tetraacylated isomers are amide rotamers around the N−CO bond. The different environment of the (e.g., 2,6-equatorial) protons in the TAD core system, *syn* or *anti* to the carbonyl oxygens, allowed demarcation of the three distinct sets in the NMR spectrum, already at room temperature. The third, small intermediate set may be due to one or more of the **B**, **C**, **F**, or **G** forms.

In a conformational VT-NMR analysis of *cis*-TECTAD (**11**) in solution, the temperature dependent behavior of the ethoxycarbonyl ^{1}H NMR signals (triplet at δ 1.21 ppm; quartet at δ 4.17 ppm) does not fit nitrogen inversion, since they (especially the quartet) would be expected to remain sharp in this range of temperatures.[24] Consequently, the dynamic conformational process was also treated as a urethane group rotation.

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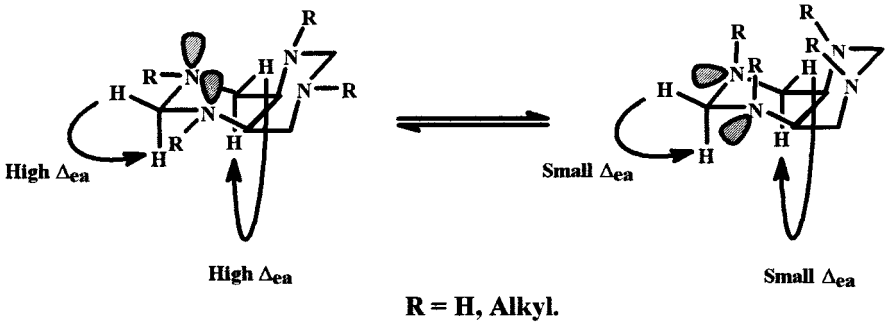
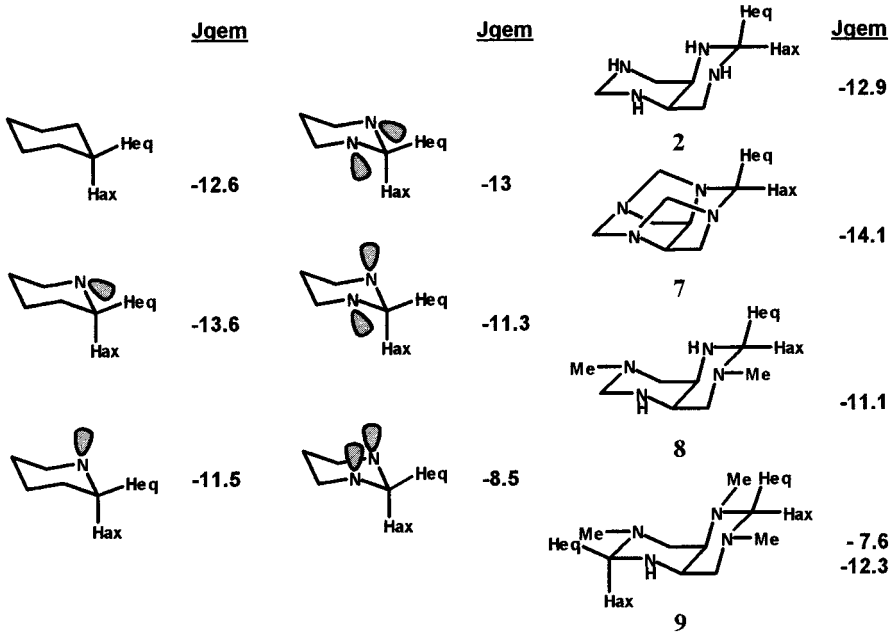
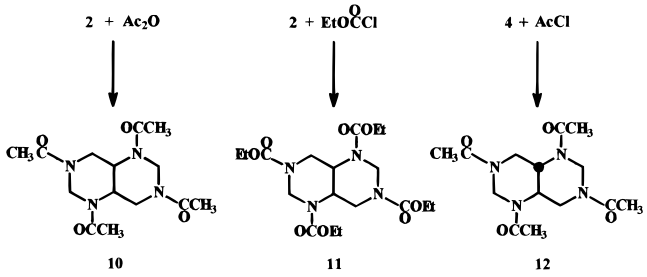
Scheme 5. Δea Criteria As Applied in *N*-Alkyl TAD Derivatives



Scheme 6. Geminal Coupling Constant (^2J) of *N*-Methylene Protons in Various 1,3-Diazane Systems (related to cyclohexane and piperidine)



Scheme 7. Acylation of *cis*- and *trans*-1,3,5,7-Tetrazadecalin



The low-field H2,6$_{eq}$ protons showed a classic process of dynamic NMR behavior of noninteracting sites, with coalescence and subsequent splitting. At $T_c = 290$ K of the lower field region, assigned to the $H_{2,6eq}$ with *anti* orientation to the carbonyl oxygens, there is a split at low temperature reaching a value of $\Delta\nu = 86.4$ Hz. At $T_c = 310$ K of the upfield region, assigned to the $H_{2,6eq}$ with *syn* orientation to the carbonyl oxygens, there is a split at low temperature reaching a value of $\Delta\nu = 151.2$ Hz. Using the approximation for the exchange rate of noninteracting sites: $K_c = \pi\Delta\nu 2^{-1/2}$ and $\Delta G^{\#}_c = 2.3RT_c[10.32 + \log(T_c/K_c)$ (Eyring equation)[28] one obtains $\Delta G^{\#}_c = 13.9$ and 14.5 kcal mol^{-1}, respectively, in excellent agreement with the known urethane free energies of rotation.

Careful examination of the spectra revealed that the averaged spectrum at room temperature transforms at 223 K into one exhibiting a ca. 1:2:1 ratio of the scrutinized sites. Following the criterion of the positive (upfield) shift induced by proximity to a negative (carbonyl) oxygen atom,[27] we concluded that most of the 10 rotameric forms exist in the mixture, without the possibility to single out specific ones.

In the *trans* system, acetylation of **4** gave 1,3,5,7-tetraacetyl-*trans*-TAD (**12**) (Scheme 7). While the *cis*-TAD derivatives undergo conformational ring inversion, the *trans*-TAD derivative (**12**) is unable to do that but can escape the strained form by ring libration. **12** was subjected to X-ray analysis, which showed (Figure 2) that it consists of two fused centrosymmetrically related boats, with the acyl groups in an *anti*−*syn*−*anti*−*syn* arrangement.

An examination of the average value of the bond angles around each N atom reveals that the values obtained for N(1) and N(3) (i.e., $\Sigma\alpha_1 = 116.6°$ and $\Sigma\alpha_3 = 117.9°$) are significantly lower than 120°. At the same time, the least planar *N*-acetyl groups, involving N(1) and N(5), are

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(28) *Introduction to Stereochemistry and Conformational Chemistry*; Juaristi, E., Ed.; Wiley & Sons: New York, 1991.

Table 6. VT-^{1}H NMR Spectra (360 MHz, δ ppm, J Hz) of *cis*-TATAD (10) and *cis*-TETAD (11)

		$H_{2,6}$		$H_{4,8}$			
		eq	ax	eq	ax	$H_{9,10}$	R[c]
10[a]	D						
	at 298 K	6.10	3.93	4.78	3.51	3.82	2.28; 2.16
		$^2J = 13.3$	$^2J = 13.3$	m	$J =$	12.4	$^3J = 13.6$
							$^3J = 3.9$
	at 228 K	6.12	3.93	4.79	3.57	3.80	2.29; 2.18
		$^2J = 13.4$	$^2J = 13.4$	m	$^2J = 11.9$	$^3J = 13.3$	
					$^3J = 13.3$	$^3J = 4.0$	
	A						
	at 298 K	6.24	4.02	4.57	3.18	3.75[d]	2.22; 2.18
		$^2J = 13.3$	$^2J = 13.3$	$^2J = 12.8$	$J = 12.1$		
				$^3J = 3.2$			
	at 298 K	6.24	4.03	4.57	3.20	3.80[d]	2.23; 2.20
		$^2J = 13.9$	$^2J = 13.9$	$^2J = 13.4$	$J = 12.3$		
				$^3J = 4.0$			
11[b]	at 333 K	6.18	3.81	4.18	2.94	4.64	4.18; 1.23
	at 299 K	6.32; 6.11	3.75	4.23	2.89	4.58	4.17; 1.21
	at 223 K	6.72; 6.48; 6.05	3.72	4.44	2.76	4.96; 4.60	4.08; 1.15

[a] In $CDCl_3$. [b] In toluene-d_8. [c] R = acetyl in **10** and ethoxycarbonyl in **11**. [d] Unresolved signal.

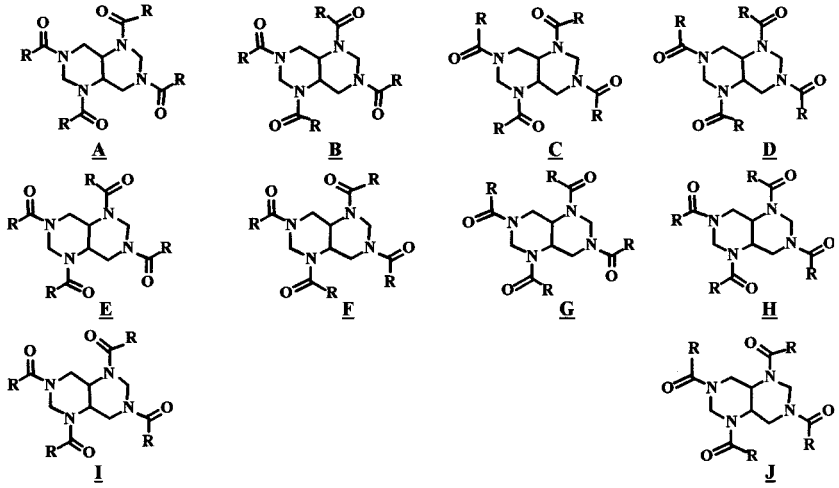

Table 7. All Possible *N*-Acyl Rotameric Forms of 10 and 11, Symmetries and Expected ^{1}H NMR Intensity Ratios, and Chemical Shifts of the $H_{2(6)eq}$ Doublets

N-acyl rotamers in **10** and **11**[a]						ratio and chem. shift of $H_{2(6)eq}$		
type	N1	N3	N5	N7	sym.	low field	intermed.	upfield
A	*anti*	*anti*	*anti*	*anti*	C_2	2		
B	*syn*	*anti*	*syn*	*anti*	C_2		2	
C	*anti*	*syn*	*anti*	*syn*	C_2		2	
D	*syn*	*syn*	*syn*	*syn*	C_2			2
E	*syn*	*anti*	*anti*	*anti*	C_1	1	1	
F	*anti*	*syn*	*syn*	*anti*	C_1		1 + 1	
G	*syn*	*anti*	*syn*	*syn*	C_1		1	1
H	*syn*	*syn*	*anti*	*anti*	C_1	1		1
I	*anti*	*syn*	*anti*	*anti*	C_1	1	1	
J	*anti*	*syn*	*syn*	*syn*	C_1		1	1

[a] *syn* and *anti* define the orientation of the carbonyl oxygen with respect to C_2 (C_6).

Table 8. Summary of Crystal Data for Compounds 4 and 12

	4·4H_2O (at 100 K)	**12**
formula	$C_6H_{22}N_4O_4$	$C_{14}H_{22}O_4N_4$
weight	214.164	310.35
crystal system	monoclinic	monoclinic
space group	$P2_1/c$	$C2/c$
a, (Å)	6.020(30)	15.595(2)
b, (Å)	8.730(1)	5.489(1)
c, (Å)	11.667(2)	17.876(2)
α, deg	90.00	90.00
β, deg	102.58(2)	92.49(1)
γ, deg	90.00	90.00
V, Å^3	598.4(3)	1528.8(4)
Z	4	4
D_{calc}, g cm^{-3}	1.189	1.348
μ(Mo Kα) cm^{-1}	0.97	1.00
F(000)	236	664
unique reflections	1363	1560
obs reflections, $>4\sigma$	1230	1350
R for obs reflections	0.047	0.042
R for all unique reflections	0.051	0.049
S	1.12	1.09

associated with the longest N−C_{aminal} bonds while the most planar amide groups, involving N(3) and N(7), have the shortest N−C bonds within the corresponding TAD system.

Conclusions

We have prepared and fully characterized *cis*- and *trans*-1,3,5,7-tetraazadecalin (TAD) (**2** and **4**) and the *N*-Me (**7**−**9**) and *N*-acyl (**10**−**12**) substituted derivatives. The X-ray structures of **4** and **12** and the conformational equilibria of **2** and **11** were analyzed. Relative stabilities and geometrical parameters were obtained from QM ab initio and molecular mechanics computations and were compared with experiment. The regular TAD compounds occur (in accord with the anomeric effect) with preferred 1,5-diaxial or tetraaxial N−H bonds and *cis*-TAD prefers the Ninside form. The N-acylated TAD derivatives, however, prefer the Noutside form in the *cis*-TAD series and the double twist boat form in the *trans*-TAD series.

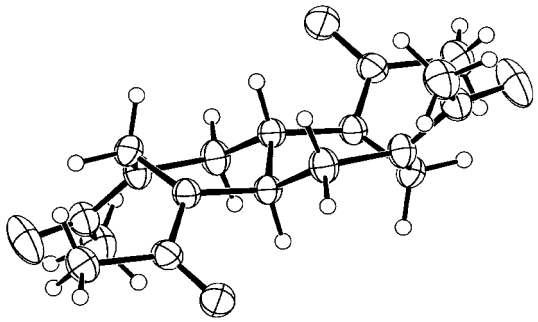

Figure 2. ORTEP drawing from the X-ray analysis of 1,3,5,7-tetraacetyl-*trans*-1,3,5,7-tetraazadecalin (**12**) with 50% probability ellipsoids of the non-hydrogen atoms.

The MM2-AE (modified for the anomeric effect in N−C−N-containing molecules) and MM3 force fields were established to be reliable tools for these systems, for use with large host systems of this kind, now under active investigation.[1b,31]

Experimental Section

General. All reactions were carried out in dry solvents under Ar and monitored by TLC and/or by ^{1}H NMR. Column chromatography was performed on Merck silica gel (60, particle size 0.040−0.063 mm). Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Satisfactory elementary analyses (Microanalytical Laboratory, Hebrew University, Jerusalem) and/or high-resolution mass spectrometric analysis have been obtained for all new compounds. Mass spectra (EI-MS, CI-MS, and FAB) and HRMS were recorded on a VG Autospec 250 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on either AC 200 or AMX 360 Bruker spectrometers and referenced to TMS. Definite assignments were based on NOE experiments. IR spectra were recorded with a Nicolet 205 FTIR instrument in KBr pellets. Commercially available reagents and solvents were purified and dried when necessary by used methods.

***cis*-(*rac*)-1,3,5,7-Tetraazadecalin (2).** A solution of 37% CH_2O (0.3 g, 3.8 mmol) in ethanol (40 mL) was added slowly over 20 min at 50 °C under an inert atmosphere to a solution of (*rac*)-1,2,3,4-tetraaminobutane[7] (TAB) (**1**) (0.25 g, 2.1 mmol) in ethanol (60 mL). The mixture was stirred at 50 °C for a further 50 min and then cooled to room temperature. After solvent evaporation (without heating), **2** was isolated as a yellowish oil, in quantitative yield (crude). Attempts to distill the product or crystallize it from various solvents failed due to its tendency to ring open and polymerize: ^{1}H NMR (200 MHz, D_2O) δ 3.88 (d, J = 12.9 Hz, 2H, $H_{2,6eq}$), 3.49 (d, J = 12.9 Hz, 2H, $H_{2,6ax}$), 2.93 (dd, J = 14.2, 2.8 Hz, 2H, $H_{4,8ax}$), 2.83 (d, J = 14.2 Hz, 2H, $H_{4,8eq}$), 2.69 (bs, 2H, $H_{9,10}$); ^{13}C NMR (50.3 MHz, D_2O) δ 61.9, 51.6, 50.6; HRMS calcd m/z for $C_6H_{14}N_4$ [M^+] 142.121847, found 142.120799.

***trans*-1,3,5,7-tetraazadecalin (4).** A solution of 37% CH_2O (0.3 g, 3.8 mmol) in *i*-PrOH (30 mL) was added slowly over 20 min at room temperature under an inert atmosphere to a solution of *meso*-1,2,3,4-tetraaminobutane[7] (TAB) (**3**) (0.25 g, 1.9 mmol) in *i*-PrOH (50 mL). The mixture was stirred at room temperature for a further 1 h. Then the solution was treated with decolorising charcoal for 10−15 min to remove impurities and filtered while hot. After solvent evaporation (without heating), **4** was isolated as a white powder in quantitative yield (crude). Recrystallization from *i*-PrOH:benzene (3:1) gave pure and colorless crystals. *t*-TAD **4**: mp 35−37 °C, 0.24 g, 1.7 mmol 45%; ^{1}H NMR (200 MHz, D_2O) δ 3.84 (d, J = 12.7 Hz, 2H, $H_{2,6eq}$), 3.46 (d, J = 12.7 Hz, 2H, $H_{2,6ax}$), 2.95 (m, 2H, $H_{4,8eq}$), 2.42 (m, 4H, $H_{4,8ax,9,10}$); ^{13}C NMR (50.3 MHz, D_2O) δ 62.6, 60.4, 50.3. FAB-MS m/z (%) 143 (MH^+, 100); HRMS calcd m/z for $C_6H_{14}N_4$ [M]$^+$ 142.121847, found 142.121828.

***cis*-1,7:3,5-Dimethylene-1,3,5,7-tetraazadecalin (7).** In a similar reaction as for **2**, but using an excess of the aqueous formaldehyde solution or alternatively, by using **4** as starting material and adding the aqueous formaldehyde solution at room temperature, **7** is obtained. The product was purified by column chromatography (basic Alumina) and eluted with CH_2Cl_2/MeOH (9:1). **7**: mp 190−194 °C (dec), 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.39 (d, J = 14.1 Hz, 2H, $H_{2,6eq}$), 4.28 (d, J = 14.1 Hz, 2H, $H_{2,6ax}$), 4.16 (dd, J = 9.8, 1.9 Hz, $2H_{bridge}$), 4.04 (d, J = 9.8 Hz, $2H_{bridge}$), 3.22 (dd, J = 10.7, 1.9 Hz, 2H, $H_{4,8eq}$), 3.12 (dd, J = 10.7, 4.6 Hz, 2H, $H_{4,8ax}$), 3.08 (bd, J = 4.6 Hz, 2H, $H_{9,10}$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 74.8, 73.6, 59.1, 56.2; HRMS calcd m/z for $C_8H_{14}N_4$ [M]$^+$ 166.121847, found 166.122265.

N-Methylation of *cis*-TAD. Methyl iodide (5.7 g, 0.04 mol) was added to a solution of **4** (0.95 g, 6.7 mmol) in warm ethanol (30 mL) and NaOH (1.0 g, 0.04 mol). The reaction was kept overnight at 40 °C, and then ethanol was removed. The semisolid was extracted with methylene chloride, and the solution was dried with $MgSO_4$ and filtered. After removal of the solvent, the crude was purified by column chromatography (silica gel, CH_2Cl_2:EtOH:NEt_3) to give *cis*-3,7-dimethyl-1,3,5,7-tetraazadecalin (**8**) 0.05 g (4% yield) as a rather unstable colorless oil [^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (dd, J = 11.1, 1.8 Hz, 2H, $H_{2,6eq}$), 2.91 (d, J = 11.1 Hz, 2H, $H_{2,6ax}$), 2.89 (dd, J = 11.6, 1.8 Hz, 2H, $H_{4,8eq}$), 2.67 (t, J = 1.8 Hz, 2H, $H_{9,10}$), 2.24 (dd, J = 11.6, 1.8 Hz, 2H, $H_{4,8ax}$), 2.09 (s, 6H, $2CH_3$)] followed by *cis*-1,3,7-trimethyl-*cis*-1,3,5,7-tetraazadecalin **(9)**, 0.102 g (8.2% yield) as a stable colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (d, J = 11.0 Hz, 1H, H_{6eq}), 3.61 (d, J = 7.6 Hz, 1H, H_{2eq}), 3.25 (t, J = 12.3 Hz, 1H, H_{8eq}), 3.06 (d, J = 1.0 Hz, 1H, H_{6ax}), 2.88 (m, 1H, H_{4eq}), 2.73 (bs, 1H, H_{10}), 2.49 (bs, 1H, H_9), 2.32 (d, J = 7.6 Hz, 1H, H_{2ax}), 2.24 (t, J = 12.3 Hz, 1H, H_{8ax}), 2.27, 2.20, 2.15 (3s, 9H, $3CH_3$), 2.08 (dd, J = 11.6, 2.5 Hz, 1H, H_{4ax}); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 79.9, 70.5, 59.4, 55.5, 52.5, 43.0, 42.3, 39.4; EI-MS m/z (%) 184 (M^+, 3.3); HRMS calcd m/z for $C_9H_{20}N_4$ [M^+] 184.1688, found 184.1678.

***cis*-1,3,5,7-Tetraacetyl-1,3,5,7-tetraazadecalin (10).** Distilled acetic anhydride (0.51 g, 5 mmol) was added dropwise at room temperature to a suspension of **4** (0.14 g, 1 mmol) in CCl_4 (14 mL). The reaction was complete after 2 h of stirring. Removal of the solvent under reduced presure gave a yellow semisolid. The product was isolated and purified by column chromatography (silica gel, EtAc:MeOH) as white crystals. Compound **10**: mp 103−105 °C, 0.22 g, 0.71 mmol, 70%; ^{1}H NMR (200 MHz, $CDCl_3$) isomer D δ 6.10 (d, J = 13.3 Hz, 2H, H_{26eq}), 4.78 (m, 2H, $H_{4,8eq}$), 3.93 (d, J = 13.3 Hz, 2H, H_{26ax}), 3.82 (dd, J = 13.6, 3.9 Hz, 2H, $H_{9,10}$), 3.51 (t, J = 12.4 Hz, 2H, $H_{4,8ax}$), 2.28, 2.16 (2s, 6H, $2CH_3$); isomer "B" δ 6.24 (d, J = 13.3 Hz, 2H, H_{26eq}), 4.57 (dd, J = 11.5, 3.8 Hz, 2H, $H_{4,8eq}$), 4.02 (d, J = 13.3 Hz, 2H, H_{26ax}), 3.75 (2H, $H_{9,10}$), 3.18 (t, J = 12.1 Hz, 2H, $H_{4,8ax}$), 2.22, 2.18 (2s, 6H, $2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$, TMS) isomer "A" δ 169.9, 169.5, 52.0, 45.1, 42.2, 21.6, 21.0; isomer A δ 170.6, 169.2, 51.7, 50.2, 42.2, 21.6, 21.0; IR (KBr pellet, cm^{-1}) 1651.7; EI-MS m/z (%) 310 (46.5, M^+), 267 (97.5, M^+ − Ac), 180 (100, $C_9H_{16}N_2O_2$); HRMS calcd m/z for $C_{14}H_{22}N_4O_4$ [M^+] 310.164105, found 310.162017. Anal. Calcd for $C_{14}H_{22}N_4O_4$: C, 54.18; H, 7.15; N 18.04. Found: C, 54.87; H, 7.15; N, 17.37.

(29) (a) Sheldrick., G. M. *SHELXS-86 in Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddar, R., Eds.; Oxford University Press: 1985; p 175. (b) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467.

(30) Sheldrick, G. M. *SHELXL-93. Program for the Refinement of Crystal Structures from Diffraction Data*; University of Göttingen: Germany, 1993.

(31) Reany, O., Grabarnik, M., Fuchs, B. *New Diaminal Ligands with Strong Heavy Metal Ion Chelation Ability.* Submitted.

(32) We use consistently the 1,3,5,7-tetraheterodecalin nomenclature. Other possible names are (1*R*)-*cis*-2,4,7,9-tetraazabicyclo[4.4.0]-decane or (4*aR*)-(4*ar*,8*ac*)-perhydro[1,3]pyrimidino[5,6-*e*]-1,3-pyrimidine. Also, due to a minor but basic omission in the CIP rules, one cannot assign configurations to chiral *cis*-decalin (and similar) systems other than by 9,10-helicity specification. Thus, $\mathbf{2}_{Ninside}$ is (9*R*;9,10-*M*)-*cis*-1,3,5,7-tetraazadecalin.

***cis*-1,3,5,7-Tetracarboxyethyl-1,3,5,7-tetraazadecalin (11).** To a solution of **4** (1.42 g, 0.01 mol) in 1 M Na_2CO_3 (aq) (100 mL) at −10 °C was added ethyl chloroformate (4.88 g, 0.045 mol) dropwise, while stirring and keeping the temperature below 0 °C. After an additional 2 h, the solution became white and thick. Extraction of the heterogeneous mixture with CH_2Cl_2 yielded 2.8 g of crude material. After column chromatography (silica gel, petroleum ether:CH_2Cl_2), **11** was obtained as a colorless liquid, 2.0 g, 45%: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.97 (bd, J = 12.4 Hz, 2H, $H_{2,6eq}$), 4.42 (bs, 2H, $H_{9,10}$), 4.18 (m, 6H, $H_{4,8eq}$ + $2CH_2$), 3.98 (d, J = 13.4 Hz, 2H, $H_{2,6ax}$), 3.23 (bt, J = 12.4 Hz, 2H, $H_{4,8ax}$), 1.29, 1.28 (2s, 6H, $2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 154.5, 154.2, 62.2, 62.1, 52.2, 46.3, 39.7, 14.5; IR (KBr pellet, cm^{-1}) 1708; EI-MS *m*/*z* (%) 430 (20.6, M^+) 385 (16.4, $M^+ - OEt$), 357 (93, $M^+ - CO_2Et$), 227 (100, $C_{10}H_{15}N_2O_4$); HRMS calcd *m*/*z* for $C_{18}H_{30}N_4O_8$ 430.2210, found 430.2087. Anal. Calcd for $C_{18}H_{30}N_4O_8$: C, 50.23; H, 7.02; N, 13.02. Found: C, 50.06; H, 6.95; N, 13.14.

***trans*-1,3,5,7-Tetraacetyl-1,3,5,7-tetraazadecalin (12).** To a suspension of **4** (0.15 g, 1 mmol) in CH_2Cl_2 (20 mL) and 40% NaOH (aq) (3 mL) was added a solution of redistilled acetyl chloride (0.3 mL, 4.6 mmol) in CH_2Cl_2 (40 mL) dropwise, while stirring and keeping the temperature below 0 °C. After an additional 1 h, the solution became white and thick. The heterogeneous mixture was then extracted with CH_2Cl_2/H_2O, and the two layers were separated. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the crude was crystallized from CH_2Cl_2/petroleum ether as pure colorless crystals: mp 223−5 °C (dec), 0.16 g, 0.5 mmol, 50%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.51 (d, J = 13.8 Hz, 2H, $H_{2,6eq}$) 4.79 (d, J = 13.8 Hz, 2H, $H_{2,6ax}$), 4.37 (dd, J = 10.9, 3.1 Hz, 2H, $H_{4,8eq}$), 4.11 (m, 2H, $H_{9,10}$), 3.38 (dd, J = 10.9, 16.5 Hz, 2H, $H_{4,8ax}$), 2.23, 2.08 (2s, 6H, $2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.3, 169.9, 53.4, 52.2, 46.9, 22.4, 21.2; IR (Kbr pellet, cm^{-1}) 1650, 1417, 1253; EI-MS *m*/*z* (%) 310 (25, M^+), 180 (100, $C_9H_{16}N_2O_2$); HRMS calcd *m*/*z* for $C_{14}H_{22}N_4O_4$ [M^+] 310.164105, found 310.163402.

X-ray Crystallography. Well-developed colorless crystals of both **4** and **12** were grown by slow evaporation from *i*-PrOH/benzene and CH_2Cl_2/petroleum ether, solutions, respectively. Single-crystal data collections of **4** were performed at 100 K and of **12** at ca. 298 K on an automated CAD4 diffractometer equipped with a graphite monochromator, using Mo Kα (λ = 0.7107 Å) radiation. Intensity data were collected by the $\omega-2\theta$ scan mode. Possible deterioration of the analyzed crystal was tested by detecting periodically the intensities of three reference reflections from different zones of the reciprocal space and were found to be negligible during the experiment.

No corrections for absorption or secondary extinction effects were applied. The structure were solved by direct methods (SHELXS-86)[29] and refined by full-matrix least-squares (SHELXL-93).[30] Non-hydrogen atoms were treated anisotropically. All the hydrogen atoms were located on difference Fourier maps; their final positions were slightly adjusted to correspond to standard C−H bond lengths. Data for atomic coordinates, bond lengths, bond angles, and torsion angles, equivalent isotropic thermal parameters, and anisotropic thermal parameters of the heavy atoms are given in the Supporting Information.

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Supporting Information Available: Crystallographic data and ORTEP drawings for **4** and **12** and Figures 3−5 showing NMR Spectra of **10** and **11** (14 pages). "This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information."

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