Tetrahedron Vol. 47, No. 6, pp. 1013-1036, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

STRUCTURE, CONFORMATION, AND STEREOELECTRONICS OF 1,4,5,8-TETRAAZADECALINS. CHEMICAL, MULTINUCLEAR NMR AND MOLECULAR MECHANICS STUDIES.[1]

Raffaello Müller[a], Wolfgang von Philipsborn[a*], Leah Schleifer[b], Pinchas Aped[b], and Benzion Fuchs[b*]

a) Organisch-chemisches Institut, Universität Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

b) School of Chemistry[**], Tel-Aviv University, Ramat-Aviv, 69978 Tel-Aviv, Israel

(*Received in UK* 25 *October* 1990)

Abstract
We present a multidisciplinary investigation of some known and new 1,4,5,8-tetraazadecalin (TAD) derivatives. Their structure, static and dynamic conformational analysis, isomerization pathways and relative stabilities were studied using ^{1}H-, ^{13}C-, and ^{15}N-NMR techniques. Molecular mechanics calculations were carried out using the MM2 force field and an earlier modified version for N-C-N containing systems. The peculiar stereoelectronic features of the C-N-C-N-C moieties in the TAD systems are emphasized.

Introduction

Ten years ago[2] a group of substituted derivatives of the interesting 1,4,5,8-tetraazadecalin (TAD) system (**1**) has been prepared and configurationally defined. Contemporary and subsequent publications[3-10] broadened the scope of this class of compounds with preparative, structural and dynamic-conformational data. The parent molecule itself (**1** R=R'=H) had been prepared long before[11-13], and attempts for its structure determination have also been reported.[14] The simplest preparative method is that used for symmetric derivatives by reacting glyoxal with a suitably substituted ethylenediamine (Scheme 1) to give one or both of the two possible TAD isomers (**1t** & **1c**) and/or the corresponding biimidazolidine isomeric derivative (**2**).[2]

In the meantime, we became gradually aware that the structural and mechanistic features of this class of compounds are much more complex than previously thought and

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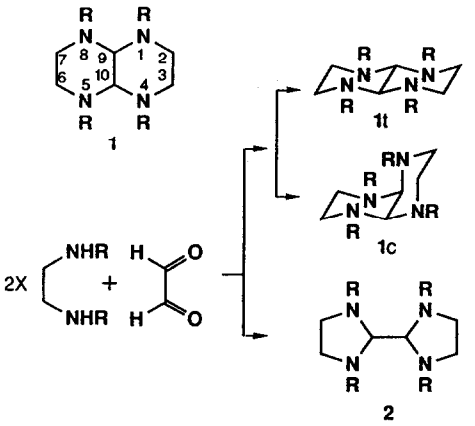
* Authors for correspondence. **Dedicated to the memory of Prof. David Ginsburg.**

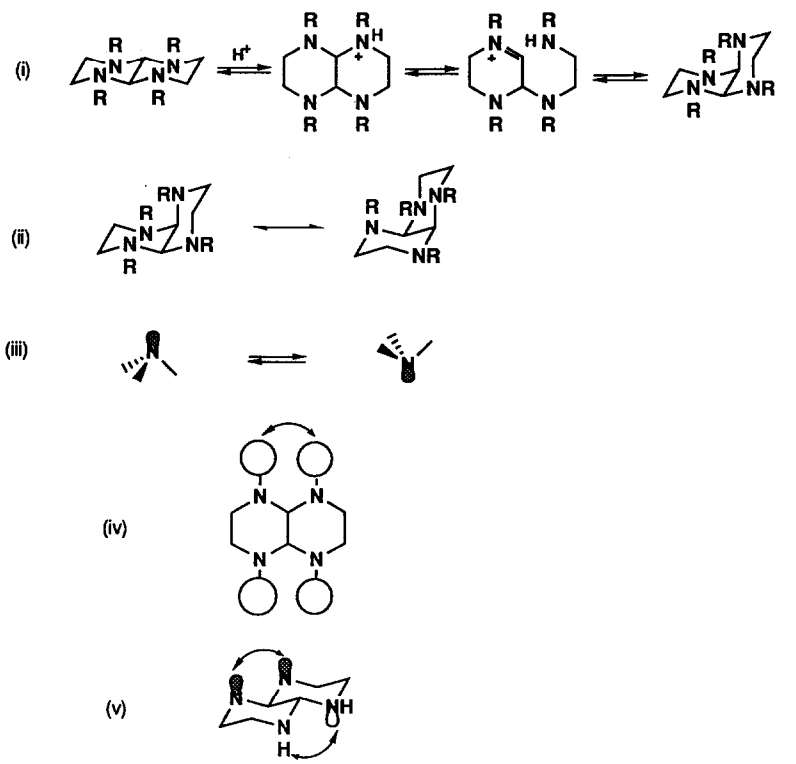
** The School of Chemistry at Tel-Aviv University is part of the Raymond and Beverly Sackler Faculty of Exact Sciences.



Scheme 1.

defined. One could understand this when considering the unusual diversity in chemical and conformational changes and effects operating in compounds in this class (Scheme 2), namely: (i) aminal ring-chain tautomerism and consequent *trans-cis* ring-system isomerization, (ii) ring inversion processes in *cis*-fused isomers, (iii) nitrogen inversion processes, (iv) steric interactions of peri-substituents, (v) lone-pair - lone-pair and n_{π}-σ^* interactions as well as N-H···:N hydrogen bonds.

Notably, the ring system (1) contains, in fact, two N-C-N moieties which belong to the X-C-Y (X,Y = hetero atoms) grouping known to exhibit peculiar stereoelectronic effects. The latter with X=Y=O were, and still are, being extensively investigated in recent years as what is



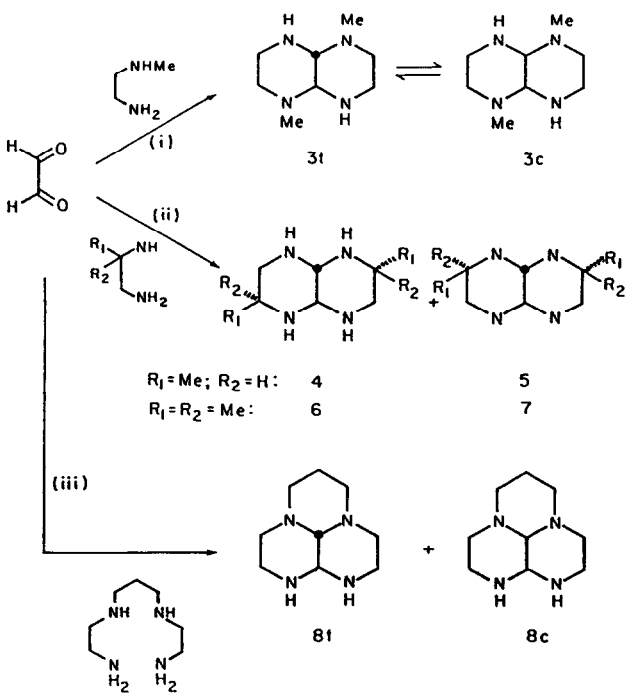
Scheme 2.

generally called the *anomeric effect.*[15] The Tel Aviv group has actively contributed to this field in both experimental and computational studies.[16-18] The most recent study, however, was actually spurred by the problems encountered in such N-C-N containing systems as the 1,4,5,8-tetraazadecalins or 1,3-diazans.[4] It dealt with the reparameterization of Allinger's MM2 force field[19] for calculation (energy and structure) of N-C-N groupings, taking into account stereoelectronic effects; these had not been included in the parameterization of MM2 for amines [20]. It was clear to us that our study of 1,4,5,8-tetraazadecalins should include such stereoelectronic considerations.

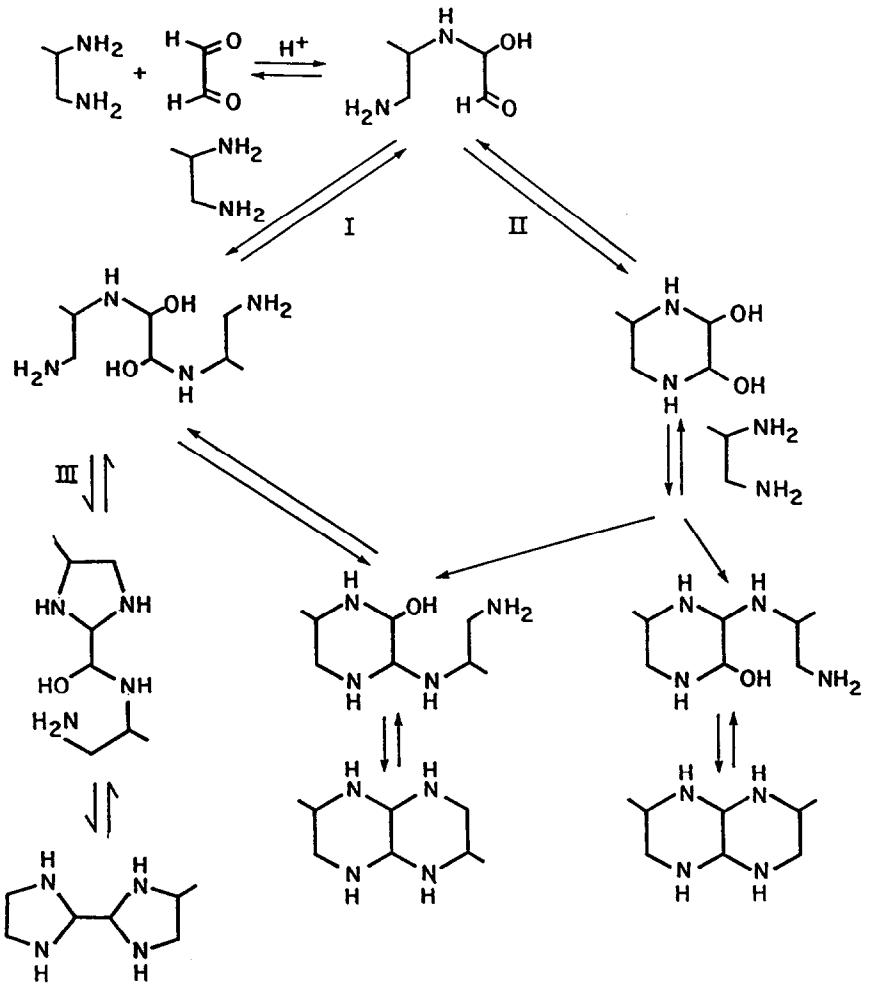
Results and Discussion

We included in this study only symmetrically substituted TAD derivatives. Hence, of the possible preparative methods[2] only the one involving condensation of glyoxal with correspondingly substituted ethylenediamines was used. The results are shown in Scheme 3, as assigned on the basis of the NMR data given and discussed below. Compound **3t** had been obtained by route (i)[2] but not well enough characterized for definitive assignment, while in the processes (ii) only the 2,6-substituted derivatives **4** and **6** had been isolated.[2] The formation of the additional 2,7-substituted isomers (**5** and **7**) are indicative of the occurrence of both possible pathways (I and II in Scheme 4) in the postulated mechanistic sequence of reversible steps.

Scheme 3.



Scheme 4.



NMR measurements, structural assignments, and isomer interconversions.

The ^{1}H-, ^{13}C-, and ^{15}N-NMR data are assembled in Tables 1, 2 and 3, respectively. Table 1 contains mainly ^{1}H-NMR spectral data of *trans*-compounds since these were isolated in pure form whereas the *cis*-isomers were usually observed in solutions of mixed composition, which prevented reliable analysis of the ^{1}H-NMR spectra . In Table 4, the ^{15}N-NMR chemical shifts are correlated with the substitution pattern on the various TAD compounds, and in Table 5 solvent effects are examined. It should be reiterated[2] that for all the TAD derivatives, the biimidazolidine isomeric structures (cf. path III in Scheme 4) are ruled out using the criteria

Table 1 ^{1}H-NMR data of *trans*-1,4,5,8-tetraazadecalins

position / conformation / compound		2 eq	2 ax	3 eq	3 ax	9	10	11 eq	11 ax	12 eq	12 ax	Me eq	Me ax
TAD (R=H)	1t	2.94	2.79			3.24							
$^2J_{gem}$		-13.0	-13.0										
2,6-DMTAD	4		2.90	2.89	2.37	3.03						0.99	
$^2J_{gem}$				-13.4	-13.4								
2,7-DMTAD	5		2.90	2.90	2.39	2.95	3.11					1.00	
2,2,6,6-TMTAD	6			2.69	2.57	3.19						1.05	1.18
$^2J_{gem}$				-13.1	-13.1								
2,2,7,7-TMTAD	7			2.72	2.56	2.82	3.51					1.07	1.19
				-13.0	-13.0								
1,5-DMTAD in $CDCl_3$	3t	2.82	2.22	2.97	2.97	2.42						2.35	
1,5-DMTAD in toluene	3t	2.46	1.75	2.54	2.82	2.20						2.30	
$^2J_{gem}$		-11.3	-11.3	-13.6	-13.6								
BTAD in D_2O	8t	2.70	2.30	2.90	2.85	2.10	3.30	2.85	2.18	1.65	1.75		
BTAD in toluene	8t	2.35	1.95	2.52	2.90	1.57	3.39	2.60	1.79	1.20	1.90		
DBTAD in $CDCl_3$ [a]	10	2.52 (2)	3.74 (2)	3.35 (3)	2.20 (3)	3.48	3.93	– (11)	4.08 (11)	1.70 (12)	2.14 (12)	1.27[b] (13)	2.28[c] (13)
(*cis* compound)		2.35 (6)	2.43 (6)	1.93 (7)	3.06 (7)			3.93 (14)	– (14)	2.80 (15)	2.01 (15)	3.19[c] (16)	0.61[b] (16)

a) numbers in parenthesis indicate the carbon atoms in compound **10** as given in the formula.
b) methyl protons
c) methine protons

Table 2 ^{13}C-NMR data of *trans*- and *cis*-1,4,5,8-tetraazadecalins

carbon position / compound	2	7	3	6	9	10	11	13	12	Me eq	Me ax
TAD (R=H) **1**											
trans **1t**	44.6				73.0						
cis **1c**	41.0				64.9						
2,6-DMTAD t_{ee} **4**	51.8		52.4		73.8					19.2	
t_{ea}	~52	49.8	~52	47.9	74.6	68.0				19.8	17.8
2,7-DMTAD t_{ee} **5**	52.1		52.7		73.4	74.2				19.2	
t_{ea}	~52	48.7	~52	50.2	68.4	75.0				19.8	17.8
2,2,6,6-TMTAD **6**	52.2		55.8		70.0					29.0	23.8
2,2,7,7-TMTAD **7**	51.7		55.8		64.4	74.6				28.5	23.2
1,5-DMTAD **3t**											
trans in D_2O	50.9		38.4		74.7					36.4	
trans in $CDCl_3$	57.6		43.9		81.4					41.8	
1,5-DMTAD **3c**											
cis -I in $CDCl_3$, 228K	54.6		38.3		74.0					40.3	
cis -II in $CDCl_3$, 228K	46.8		44.1		72.3					41.3	
BTAD **8t**											
trans in D_2O	55.7		44.9		88.0	72.3	55.9		25.8		
trans in $CDCl_3$	54.9		43.7		88.2	71.3	53.8		24.2		
BTAD **8c**											
cis in $CDCl_3$, 223K	54.0	44.3	38.7	44.4	76.0	66.2	51.9	55.4	18.9		
DBTAD in$CDCl_3$ [a] **10**							62.0 (11)	58.2 (13)	29.9 (12)		
(*cis* compound)	46.9	37.7	49.3	48.9	78.1	64.0	58.5 (14)	52.5 (16)	27.7 (15)	19.8	13.0

a) numbers in parenthesis indicate the carbon atoms in compound **10**

of M^+:$(M/2)^+$ which is ca. 0.1 - 10 in the mass spectra of decalin structures as opposed to ca. 10^{-3} for biimidazolidine isomers. Furthermore, both the geminal and the vicinal coupling constants in the peripheral N-CH_2-CH_2-N moiety are of diagnostic value; the former are ca. -13 Hz (vs. -9 Hz in imidazolidine derivatives[2]) and the latter give a value of $R=J_{trans}/J_{cis} \approx 2$ (and not 0.6, as typical for five-membered rings).[21] Non-chair conformations ($R=J_{trans}/J_{cis} \approx$ 1.5) could be similarly excluded.

***trans*-1,4,5,8-Tetraazadecalin (TAD) (1t , R=H).**

The previously reported ^{1}H- and ^{13}C-NMR data were largely reproduced (with only small differences in the ^{13}C chemical shifts due to slightly different solvent/reference) and suggest a rigid *trans* geometry, mainly since the coupling constants in the AA'BB' peripheric CH_2-CH_2 grouping are 12.1, 3.6, and 1.5 Hz. The single ^{15}N-resonance at -331.5 ppm fits nicely in this picture.

There is, however, a new observation. After about six days in water at room temperature, a new ^{15}N-resonance appears at higher field, -339.8 ppm, along with two weak ^{13}C-signals at 41.0 ppm (broad, which become sharper at higher temperature), and 64.9 ppm (sharp). The new signals attained a 1:6.5 ratio (measured at the line at 64.9 ppm) after a month and were assigned to the *cis* isomer formed in a slow isomerization process. This

Table 3 ^{15}N-NMR chemical shifts in *trans*- and *cis*-1,4,5,8-tetraazadecalins.

compound \ position of nitrogen		1	4	5	8
TAD (R=H)	1				
trans	1t	-331.5			
cis	1c	-339.8			
2,6-DMTAD	4				
tee		-316.1	-331.3		
tea [a]		-316.7 [a]	-333.7 [a]		
2,7-DMTAD	5				
tee		-315.6	-331.9		
tea [a]		-317.7 [a]	-334.6 [a]		
2,2,6,6-TMTAD	6	-308.9	-337.6		
2,2,7,7-TMTAD	7	-308.3	-337.9		
1,5-DMTAD	3t				
trans in $CDCl_3$		-332.8	-341.4		
1,5-DMTAD	3c				
cis -I in $CDCl_3$, 223K		-340.4	-342.0		
cis -II in $CDCl_3$, 223K		-334.7	-356.9		
BTAD	8t				
trans in D_2O		-324.7	-332.5		
trans in $CDCl_3$		-324.4	-331.7		
BTAD	8c				
cis in $CDCl_3$, 223K		-337.6	-333.1	-341.8	-335.4
DBTAD	10				
cis in $CDCl_3$		-334.6	-323.0	-338.7	-321.4

a : This values arise from the 8 weak lines observed in Figure 1. The doublet components at higher frequency were arbitrarily assigned to 4. In the following Tables only mean values for the doublets are given.

assignment is supported by the reported facts[5] that fast acetylation of 1t (R=H) using acetyl chloride gives the *trans*-tetraacetyl-TAD (TATAD) (1t, R=Ac) whereas acetic anhydride gives slowly a 1:3 mixture of *cis* and *trans*-TADAD (1c, 1t R=Ac).

***trans*-1,5-Dimethyltetraazadecalin (1,5-DMTAD) (3t).**

This is the only product isolated in the reaction of N-methyl-ethylenediamine with glyoxal (Scheme 3 (i)). The theoretically possible 1,8-isomer is not observed probably because it would carry strongly destabilizing peri-substituents.

The ^{1}H- and ^{13}C-NMR spectra were fully analyzed using selective decoupling and SFORD techniques, and the two ^{15}N-resonances fit nicely the *trans*-assignment. However, after about 24 hours in chloroform at room temperature an apparent equilibrium was established with two new, apparently *cis* species, four ^{15}N-signals of which appear, two of them particularly broadened. Eventually, in a variable temperature study in $CDCl_3$, the dynamic behaviour could be analyzed. At 297 K, the ^{15}N-H resonances of the *cis* isomeric species coalesce; on cooling they split into two signals attaining a $\Delta\delta$ of 14.9 ppm. The ^{13}C spectrum shows below coalescence, at 228 K, eight sharp signals (in addition to those of the original *trans* isomer). These were assigned to the two diastereoisomeric *cis*-I and *cis*-II compounds, which interconvert each with the other's enantiomer by a *cis*-decalin type ring-

Table 4 ^{15}N-NMR data of *trans*- and *cis*-1,4,5,8-tetraazadecalins: chemical shifts vs position of ring substituents

relative position of substitution / compound			α	β_{eq}	β_{ax}	β_{eq+ax}	γ_{eq} (anti)	γ_{ax} (gauche)	γ_{eq+ax}	$\alpha+\beta_{eq}+\gamma_{eq}$	$\alpha+\beta_{ax}+\gamma_{eq}$
TAD in D_2O	1										
trans	1t	-331.5									
cis	1c	-339.8									
2,6-DMTAD in D_2O	4										
tee				-316.1			-331.3				
tea [a]				-317	-325		-334	-340			
2,7-DMTAD in D_2O	5										
tee				-315.6			-331.9				
tea [a]				-317	-325		-334	-340			
2,2,6,6-TMTAD in D_2O	6					-308.9			-337.6		
2,2,7,7-TMTAD in D_2O	7					-308.3			-337.9		
1,5-DMTAD	3t										
trans in $CDCl_3$			-332.8				-341.4				
1,5-DMTAD	3c										
cis -I in $CDCl_3$, 223K			-340.4				-342.0				
cis -II in $CDCl_3$, 223K			-334.7				-356.9				
BTAD	8t										
trans in D_2O		-332.5								-324.7	
trans in $CDCl_3$		-331.7								-324.4	
BTAD	8c	-333.1									
cis in $CDCl_3$, 223K		-341.8								-337.6	-335.4
DBTAD	10									-334.6	-323.0
cis in $CDCl_3$										-338.7	-321.4

a) see footnote of table 3; cf. formula 11.

inversion coupled with N-inversion (Scheme 5). The diastereoisomeric interconversion partners *cis*-I and *cis*-II are, hence, not equally populated. The *trans-cis* interconversion (Scheme 5) is bound to occur by way of aminal ring-chain tautomerism (Scheme 2 (i)), in a relatively slow process on this time scale.

In this triple-equilibrium mixture at 228 K in $CDCl_3$ solution, the isomeric ratio is about: 10-(*trans*):4-(*cis*-I):6-(*cis*-II). The free-energies of activation for interconversion of non-equally populated species in the *cis* series were calculated using the known approximations [22].

$$\Delta G^{\neq}_{cisII} = 4.57 \cdot T_c \cdot \left[10.62 + \log \frac{X}{2\pi(1-\Delta P)} + \log \frac{T_c}{\Delta \nu} \right] \qquad \text{(i)}$$

$$\Delta G^{\neq}_{cisI} = 4.57 \cdot T_c \cdot \left[10.62 + \log \frac{X}{2\pi(1+\Delta P)} + \log \frac{T_c}{\Delta \nu} \right] \qquad \text{(ii)}$$

where $P_{II} - P_I = \Delta P = [(X^2 - 2)/3]^{2/3} \cdot 1/X$ and $X = 2\pi\Delta\nu\tau = 1.88$, P_I and P_{II} being the relative populations of *cis*-I and *cis*-II, respectively, and $1/\tau = 1/\tau_I + 1/\tau_{II} = 1923$, where τ_I and τ_{II} are

lifetimes of I and II, respectively, defined and calculated according to ref. 22. The results for the free-energies of activation $\Delta G^{\neq}$ are presented in Table 6 . Hence, the relative stabilities: $\Delta G°_{trans \rightarrow cis\text{-II}} \approx 0.54$ and $\Delta G°_{cis\text{-II} \rightarrow cis\text{-I}} \approx 0.24$ kcal/mol, in excellent agreement with the observed composition.

Notably, on slow evaporation the *trans* isomer is exclusively and quantitatively isolated in crystalline form.

***trans*-2,6- and *trans*-2,7-Dimethyltetraazadecalin (4 and 5, respectively).**

These DMTAD compounds were observed in the analysis of the reaction product of 1,2-diaminopropane with glyoxal (Scheme 3 (ii)). The presence of two isomers is clearly indicated by the different ^{13}C-NMR spectra, e.g., there is only one signal for the carbon atoms C9 and C10 of one isomer (2,6) and it is right between the two of the second (2,7) isomer; the vicinal coupling constants ($^3J = 3.0$, $^3J' = 2.1$ Hz) of the proton α to the decoupled methyl group indicated that the latter is equatorial. (This is supported by the results from ^{13}C-NMR spectra of the tetramethyl derivatives **6** and **7** treated below.) The ^{15}N-spectrum shows accordingly two pairs of signals. After some time, however, four additional pairs of signals appeared reaching about 10% of the total. The spectrum is shown in Figure 1, to exemplify the ^{15}N-NMR spectra we dealt with in this work. The rationalization of the above spectral changes is not too simple and is best done by examining Scheme 6 where all species of 2,6- and 2,7-DMTAD are depicted, with special emphasis on the possible combinations between two chiral 2-methylethylenediamine units to condense with glyoxal to yield the end product. Our criteria are mechanism, relative stability, symmetry, and NMR spectral data.

Scheme 5.

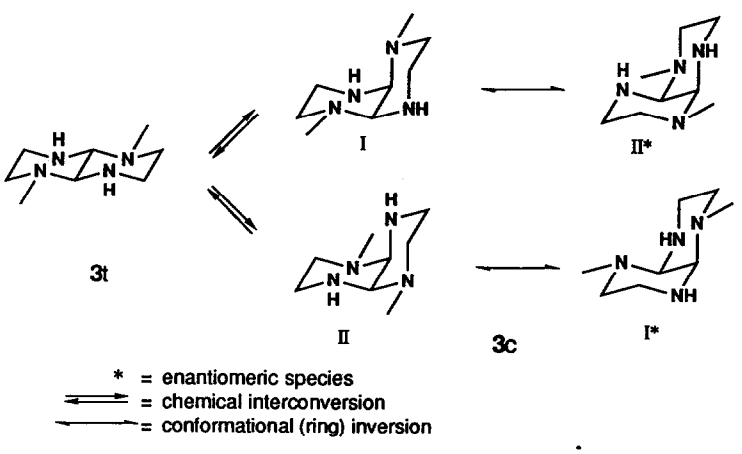


Table 5 Substituent parameters for ^{15}N chemical shifts in azadecalins : comparison between data determined in polar solvents (tetraazadecalins[a]) and in cyclohexane (decahydroquinolins[b]); cf. also formula **11**.

solvent / substitution on N	polar (D_2O and $CDCl_3$) [a]	non polar (cyclohexane) [b]
α_{eq}	-1.3 (1)	-6.2 (2) [c]
α_{ax}	—	-23.5 (1)
β_{eq}	+15.3 (4)	+17.6 (2)
β_{ax}	+7.0 (2)	+8.7 (1)
γ_{anti} (equatorial)	-1.2 (4)	0.0 (6)
γ_{gauche} (axial)	-9.1 (4)	-8 ÷ -10
$\beta_{Neq\text{-}C\text{-}Nax}$	-1.6 (1)	—
$\gamma_{Nax\text{-}C\text{-}C\text{-}Nax}$ (gauche)	-2 ÷ -8	—

a) This work.
b) Ref. 30.
c) The value in parenthesis indicates the number of cases.

Table 6 Free-energies of activation for ring inversion in compounds 3c and 8c.

Compound: 3c		Temp. [K]	C(9,10)	C(2)	C(3)	Me
$\delta(^{13}C)$		318	73.7	50.5	42.4	41.1
$\delta(^{13}C)$(*cis*-I)		228	74.0	54.6	38.3	40.3
$\delta(^{13}C)$(*cis*-II)		228	72.3	46.8	44.1	41.3
$\Delta\nu$	[Hz]	228	178.5	784.8	577.4	95.4
T_c	[K]		260 ± 2	280 ± 5	276 ± 5	254 ± 2
$\Delta G^{\neq}$(*cis*-II)	[kcal/mol]		12.3 ± 0.1	12.5 ± 0.2	12.5 ± 0.2	12.3 ± 0.1
$\Delta G^{\neq}$(*cis*-I)	[kcal/mol]		12.1 ± 0.1	12.2 ± 0.2	12.2 ± 0.2	12.1 ± 0.1

Compound: 8c		Temp. [K]	C(2), C(7)	C(3), C(6)	C(11), C(13)
$\delta(^{13}C)$		323	49.9	42.2	54.3
$\delta(^{13}C)$		223	44.3	44.4	55.4
$\delta(^{13}C)$		223	54.0	38.7	51.9
$\Delta\nu$	[Hz]	223	975.9	573.5	352.1
T_c	[K]		305 ± 5	295 ± 5	290 ± 5
$\Delta G^{\neq}$	[kcal/mol]		13.0 ± 0.2	12.9 ± 0.2	12.9 ± 0.2

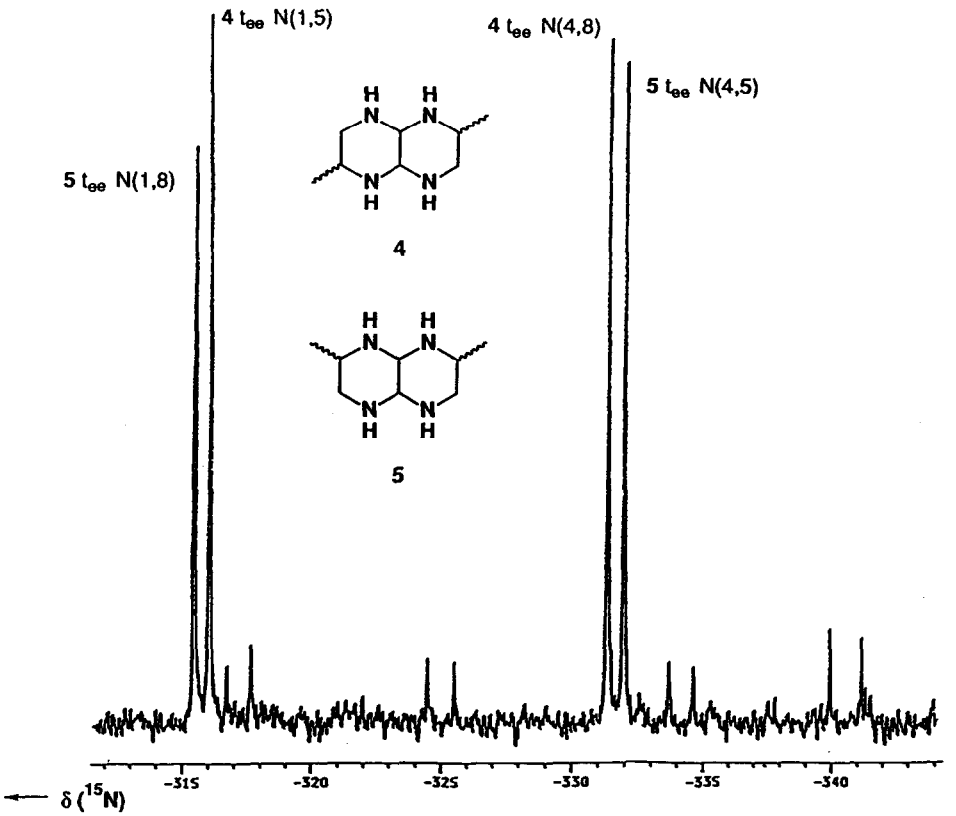
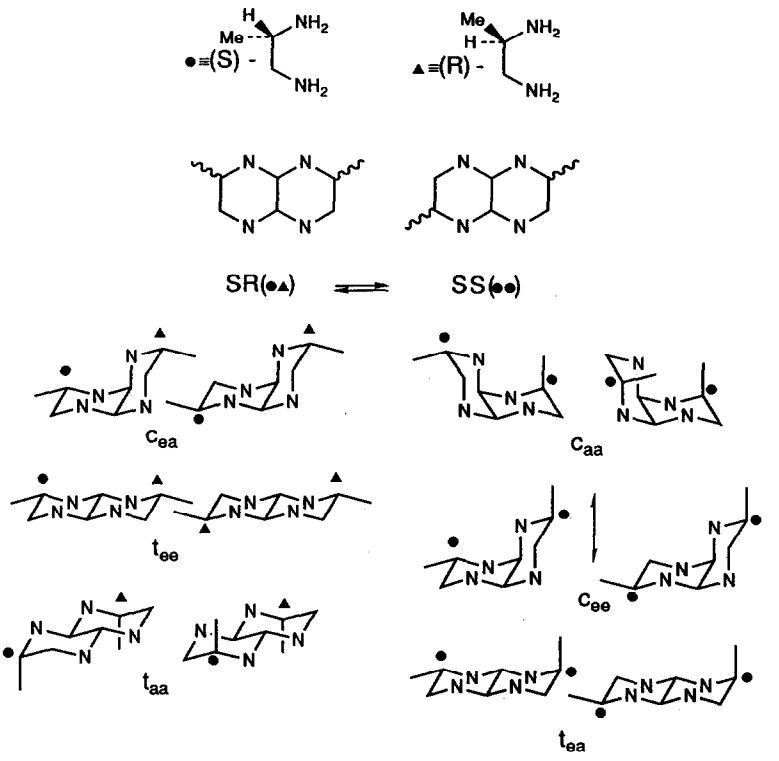


Figure 1: ^{15}N-NMR spectrum (40.6 MHz, proton noise-decoupled) of 2,6- and 2,7-dimethyl-*trans*-1,4,5,8-tetraazadecalin (4 and 5, respectively), D_2O/DMSO-D_6 (6:4) four weeks after dissolution. Strong signals arise form the two t_{ee} isomers, weak signals from the t_{ea} isomers.

We work, of course, with racemic starting material which, according to the NMR spectral data, gives two symmetric, i.e., meso(*R*,*S*) *trans* products: the 2,6-isomer belongs to the C_i point group and the 2,7-isomer to the C_s one (the diequatorial forms "*tee*" are, of course, preferred in each case over the diaxial "*taa*" ones). The most likely species to account for the four additional pairs of signals are, by all criteria, the "*tea*" forms with no symmetry (C_1), i.e., racemates. The implication is that the isomerization has to allow change of configuration at one of the asymmetric centres which can obtain only in a path II type (Scheme 4) with removal and recondensation of a methylethylenediamine unit. Assuming near equilibrium compositions and similar T_2 and T_1 relaxation times for corresponding nitrogen nuclei, $\Delta G°_{tee \rightarrow tea} = RT\ln K \approx 1.4$ kcal/mol. This is quite similar to the conformational free energy difference of an equatorial vs. axial 3-methyl group in piperidine and N-methylpiperidine (1.5 - 1.6 kcal/mol)[23,24] (we decided not to invoke $RT\ln 2 \approx 0.4$ in favour of tea as an entropy of mixing

Scheme 6.



term due to the fact that *tea* is a d,l pair, and both isomers are bound to exist in a variety of symmetry breaking forms due to the numerous combinations of N-H conformations, which are difficult to assess accurately at this stage). Hence the value of 1.4 kcal/mol is then taken as the free energy difference of an equatorial vs. axial methyl group in TAD: somewhat less than in cyclohexane since there is one less 1,3-Me-H interaction, but higher than expected on that account presumably due to the shorter C-N bonds.

2,2,6,6- and 2,2,7,7-Tetramethyl-*trans*-1,4,5,8-tetraazadecalin (6 and 7).

These (TMTAD) derivatives are the ultimate result of the reaction of 1,2-diaminoisobutane with glyoxal. Initially - as reported[2] - 2,2,6,6-tetramethyl-tetraazadecalin (**6**) was the only isolated product. After one day, however, one could detect in the NMR spectra the appearance of a second product, identified (vide infra) as the 2,2,7,7-isomer (**7**).

Again, differentiation was possible using ^{1}H-, ^{15}N- and ^{13}C-NMR and symmetry criteria. For example (Figure 2), **6** has C_i symmetry, hence, a singlet at 70.0 ppm for the carbon atoms C9 and C10, while **7** has C_s symmetry with two such signals for the respective carbons (Figure 2a). A ^{13}C-gated decoupling NMR measurement (Figure 2b) showed the 70.0 ppm singlet split into a double doublet with ^{1}J = 150 Hz and ^{3}J = 8.8 Hz. The latter is due to long range coupling with the equatorial proton on C7 (or C3). At the same time,

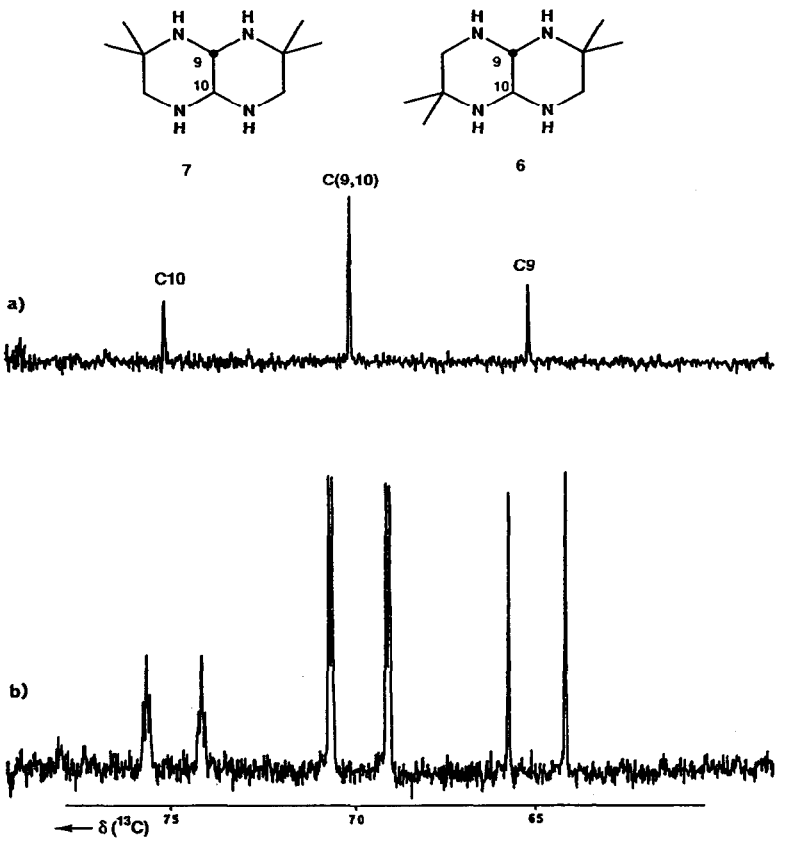


Figure 2: ^{13}C-NMR spectra (90.6 MHz) of the bridgehead C9-C10 grouping of 2,2,6,6- and 2,2,7,7-tetramethyl-*trans*-1,4,5,8-tetraazadecalin (**6** and **7**, respectively), in D_2O : a) proton noise-decoupled; b) proton coupled.

the C9 and C10 of **7** appear as a doublet at 64.6 ppm (^1J= 143.8 Hz) and a double triplet at 74.7 ppm (^1J= 142.4 Hz, ^3J= 8.6 Hz), respectively. Obviously, C10 has two equatorial protons three bonds away, while C9 has none. It is worth noting that the C-X-C-H $^3J_{C-H}$ coupling constants are known in case of X=C or O to be maximal at a dihedral angle of 180° and very small at 90° [25]. This is now confirmed for X=N, since $^3J_{C-H,\ eq}$ is well observed, but not $^3J_{C-H,\ ax}$.

The **6**→**7** isomerization as well as the **4**→**5** one (vide supra) can take place only as depicted in Scheme 4 - path II.

Concluding this discussion of peripherally substituted tetraazadecalins, and as a result of the findings that 2,7 isomers accompany the 2,6 ones, along with definite regio- and stereoisomerization processes, it is important to reemphasize the point made by Willer[6b] concerning the addition of path II to the formerly postulated[2] reaction modes (Scheme 4).

1,8-(1',3'-Propylidene)-*trans*- and *cis*-1,4,5,8-tetraazadecalin (8t, 8c).

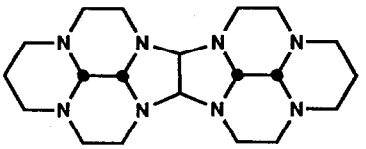
This 1,8-bridged tetraazadecalin system (BTAD) had been obtained[2] from the reaction of 1,4,8,11-tetraazaundecane with glyoxal (Scheme 3 (iii)). It has been proposed to occur as two configurational isomers (albeit without resolution) in the ratio 8t:8c ≈ 4:1. Subsequently, an NMR-analysis of the conformational dynamics of the *cis* isomer (8c) was reported[26] (see also below), We decided to elaborate the study of this interesting system using a variety of approaches.

First, resolution was carried out to isolate the pure *trans* (8t) but only the enriched *cis* (8c) isomers. Equilibration studies were not straightforward. In water at 88° pure *trans* isomer (8t) was readily obtained from both samples. In aprotic solvents like toluene and nitrobenzene, isomerization from both directions was observed but at a much slower rate (several days), even at 100° and higher. However, accurate equilibrium could not be established due to faster decomposition, and only limiting thermodynamic values were calculated.

At 110° in toluene and after 50 hours, the equilibration mixtures from 8t→8c reached 12:1 and from 8c→8t 1:7 before extensive deterioration. These results lead to a free energy difference range of 1.5 - 1.9 kcal/mol in favor of the *trans* isomer (8t).

A full assignment of the ^{1}H-NMR spectrum of 8t was achieved by a COSY45 experiment and C,H correlations in D_2O, while the *cis* isomer (8c) exhibits broad signals due to slow ring inversion at room temperature. The inversion was frozen out at low temperature and the site-exchange was studied by ^{13}C-NMR (at 100.6 MHz). Coalescence was observed at T_c = 295 K for the signals of C3(C6) which split at lower temperature reaching a value of $\Delta\delta$ of 5.7 . Using the approximation for the exchange rate of non-interacting sites $k = \pi\Delta\delta/\sqrt{2}$ and $\Delta G_c^{\neq} = 4.57 \cdot T_c \cdot [10.2 + \log(T_c/k)]$ (Eyring equation) one obtains $\Delta G^{\neq} = 12.9 \pm 0.2$ kcal/mol, in excellent agreement with Riddell's value of $\Delta G^{\neq}(279 \pm 5\ K) = 13.2 \pm 0.3$ kcal/mol.[26] At the same time, an analogous ^{15}N-NMR study (at 40.56 MHz, Figure 3) gave for >NH, with $\Delta\delta$ = 8.7 and $T_c \approx 292 \pm 5$ K, a value of $\Delta G^{\neq} = 13.0 \pm 0.2$ kcal/mol, respectively.

In attempts to isolate pure isomers of 8 from their reaction mixture, crystals were deposited after long standing. These, however, showed a molecular ion of m/z = 386 in the mass spectrum (in contrast to the expected 182) and an additional singlet at 4.16 ppm in the ^{1}H-NMR spectrum (otherwise very similar to that of 8c). These data indicated that we deal with a CH-CH bridged dimer of 8, i.e., bis[1,8-(1',3'-propylidene)-*cis*-1,4,5,8-tetraazadecalin]-*cis*-1",2"-ethylidene.



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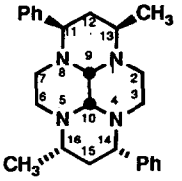

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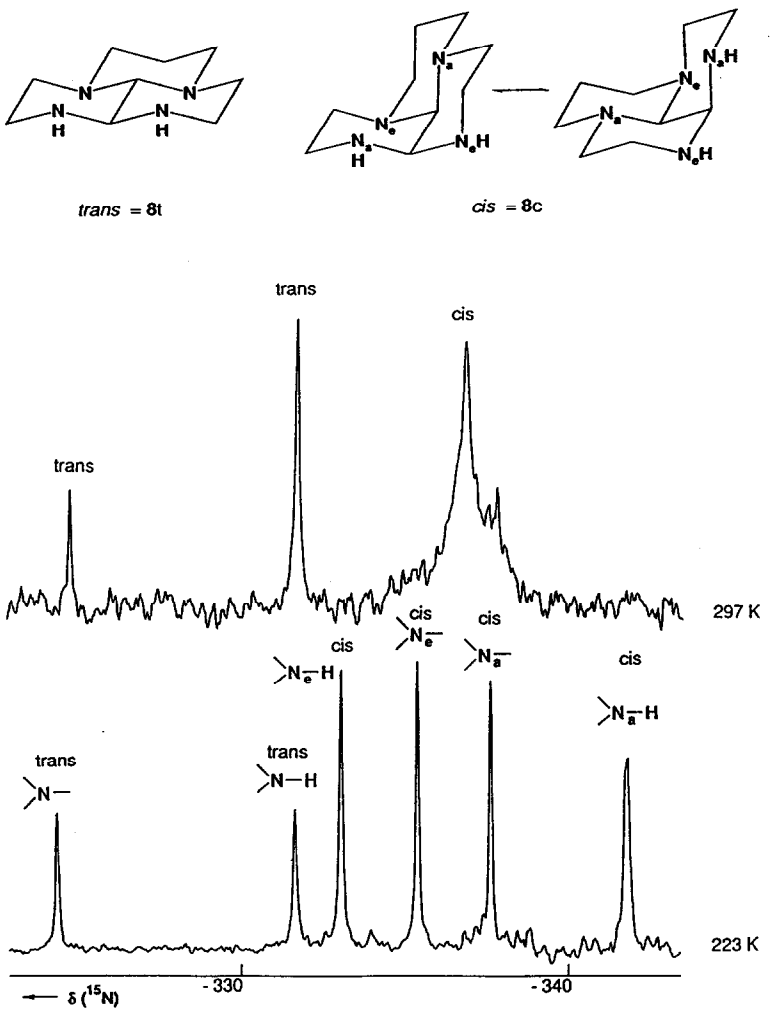


Figure 3: Variable temperature ^{15}N-NMR spectrum (40.6 MHz, proton noise-decoupled) of a mixture of 1,8-(1',3'-propylidene)-*trans*-- and -*cis*-1,4,5,8-tetraazadecalin (8t and 8c respectively) in $CDCl_3$/DMSO-D_6.

However, only after having succeeded in performing an X-ray diffraction analysis[27] was the configuration of the ethylidene bridged safely assigned to be 1",2"-*cis*, i.e., **9**. Evidently, the latter was formed by condensation of 8c with residual glyoxal.

(8,1)(4,5)-Bis-(1',3'-phenylbutylidene)-*cis*-1,4,5,8-tetraazadecalin (10)

This doubly-bridged tetraazadecalin system (DBTAD) had been described by Turner and coworkers[10a] who obtained it using method iii from Scheme 3. The configuration at the various centres of this compound, i.e., the *cis* -fused TAD structure and the *cis-anti-cis*

relationship of the two substituent pairs, were demonstrated by an X-ray study in the same work[10a] and confirmed also by the NMR spectroscopic studies in the present work. Assignment of all proton and carbon resonances was achieved by combined use of one- (selective irradiation) and two-dimensional (proton detected multiple quantum heteronuclear $^{1}H,^{13}C$-correlation) techniques. Variable temperature NMR measurements showed only a sharpening of signals at higher temperatures and no signal splitting at low temperatures. It appears that the molecule does not undergo fast ring inversion (on the NMR time-scale) except for a chair-twist-boat libration. The latter, energetically inexpensive process may achieve relief of the 1,3-diaxial Ph---Me interaction. The assignment of the four nitrogen resonances is based mainly on the $N_{axial}/N_{equatorial}$ criterion and on the trend in the ^{15}N correlation with ^{13}C chemical shifts in decalin analoga (see below).

NMR-chemical shifts.

The ^{13}C-NMR data (Table 2), both old[2] and new, conform largely with the known substituent -parameter additivity schemes in saturated N-heterocycles[23,28a,29]. The γ-effect is here predominant and can readily be observed in the relative shielding of carbon nuclei *gauche* (as compared to *anti*) to vicinal carbons in C-C-C-C and even more so in C-C-N-C systems. These effects can be expressed in numbers: a γ-gauche interaction causes shielding by more than 5 ppm and a γ-anti interaction shielding by less then 1 ppm for ^{13}C. Some examples are the axial methyl groups in the tetramethyl derivatives (**6** and **7**) which resonate more than 5 ppm upfield from the equatorial ones, similarly so the C9 nucleus in **6** and twice as much C9 in **7**, as expected from a double γ-effect on it. Another instructive example is the C12 nucleus in **8c** which is about 5 ppm upfield from C12 in **8t**.

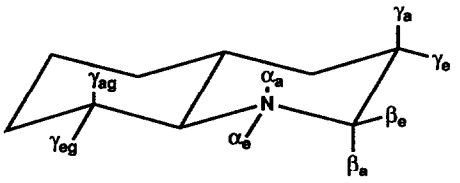
There is a linear correlation between the ^{13}C chemical shifts in the TAD's and in the corresponding decalins. Such correlations are already known for alkyl amines[29b,c].

Carbons with 1 α-N :	$\delta(^{13}C,TAD) = 25.744 + 1.129 \cdot \delta(^{13}C,decalin)$	r= 0.94
Carbons with 2 α-N :	$\delta(^{13}C,TAD) = 20.849 + 0.925 \cdot \delta(^{13}C,decalin)$	r= 0.93
Carbons with 1 β-N, without α-N :	$\delta(^{13}C,TAD) = 0.668 + 0.847 \cdot \delta(^{13}C,decalin)$	r= 0.95

Following this approach, once the δ values for a model decalin are known, experimentally or from calculation[29b], one should be able to predict the data for the corresponding TAD by using the suitable equation. The low correlation coefficients, however indicate that additional factors operate in our systems, presumably the stereoelectronic ones.

Turning to the ^{15}N chemical shifts, the experimental data are collected and analyzed in Tables 3-5. The assignments are presented in Table 3, whereas Table 4 shows the substitution pattern at the individual N-atoms relative to the parent *trans*-TAD **1t** for the *trans* series (cf. **11**) and to the parent *cis*-TAD **1c** for the *cis* series. By substituents we mean only the methyl,

methylene and methine groupings, the latter two in compounds **8** and **10**. In addition, it should be noted that one can rely on quite a comprehensive documentation of ^{15}N shielding data in simpler systems [28b,30-32].



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By referring the observed ^{15}N chemical shifts of the substituted tetraazadecalins to the parent compound **1t**, substitution increments can be extracted which are summarized in Table 5 [1f]. They are compared with literature data obtained from decahydroquinolines measured in nonpolar solvents [30].

The α-values represent the effect of a carbon directly bound to the nitrogen. It can be assumed that such a substituent will be equatorial, but it can not be absolutely excluded that, in flexible structures, it might also be in axial position for part of the time. For this reason the magnitude of this parameter is not very reliable. Two β parameters are given depending on the orientation of the substituent at the six membered ring, axial or equatorial. For the γ parameters also two types are given, γ_a for the effect of a carbon in position anti to the nitrogen, γ_g for a CH_2 group gauche to the considered nitrogen. A corresponding effect appears to be about 1 ppm more shielding for a methyl than for a methylene group, presumably in consequence of the free rotation of the CH_3 group. Where both γ_a and γ_g are present on the same atom the effect does not correspond to the sum of γ_a and γ_g, perhaps because of a deviation from the ideal chair conformation.

Another two parameters are introduced here to better distinguish between *trans* and *cis* compounds. In all the *trans* TAD (cf. **11**) β standing N-atoms are both equatorial, while those γ standing are anti. In the *cis* compounds there is always a nitrogen axial to an equatorial one (basic requirement for the anomeric effect) and both γ_a and γ_g are present: equatorial N-atoms are anti, axial N-atoms are gauche. The magnitude of the given parameter $\beta_{Neq\text{-}C\text{-}Nax}$ is small and could be isolated for only one case (**8c**, cf. Table 5). Such an upfield shift can be seen also in the ^{15}N-NMR spectra of the other derivatives, for example TAD itself (Table 3), but it can not be isolated from other interactions. The second parameter $\gamma_{Nax\text{-}C\text{-}C\text{-}Nax}$ (gauche) introduced here for the cis compounds is due to a γ effect for two gauche standing vicinal N-atoms. It is comparable in significance and magnitude to γ_g , with the main difference that on both atoms lone-pairs are present. Hence, it appears again that the γ_g effect is the most important one because of its sensitivity to variation of the conformation.

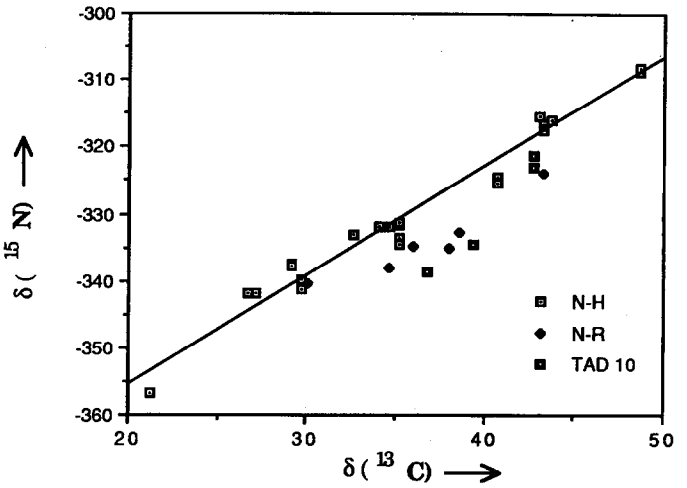


Figure 4: Correlation of ^{15}N and ^{13}C chemical shifts in tetraazadecalins and corresponding decalins. The statistical parameters are as follow:

$\delta(^{15}NH) = -388.0 + 1.62 \cdot \delta(^{13}CH_2)$, R= 0.984

$\delta(^{15}NR) = -379.0 + 1.21 \cdot \delta(^{13}CHR)$, R= 0.944

For simplicity only the line for the NH/CH_2 correlation is shown.

Finally, attempts were made to correlate ^{15}N chemical shifts of substituted tetraazadecalins with the δ(C) values of the corresponding carbon atoms in substituted decalins (Figure 4). Similar linear correlations have been reported for piperidines and tetrahydroquinolines [32], pyridines [33] and pyrimidines [34]. The correlation coefficients are still relatively low, indicating that we may miss the stereoelectronic factor in the correlation. The larger deviations from linearity of the correlation are due to **10**, a highly substituted tetraazadecalin, and thus may be caused by sterically induced chair deformations..

Molecular mechanics calculations.

We carried out molecular mechanics calculations of these systems using Allinger's MM2 force field[19,20] which we have recently modified[4], by reparameterizing it (MM2-AE) to account for the stereoelectronic effect in N-C-N containing systems, including C-N bond shortening in tertiary amines[20b] and intramolecular hydrogen bonding effects. Indeed, it was rewarding to see how well our (MM2-AE) calculated structure of 1,3-diazane matched that recently calculated ab initio (at the 4-21G level) by Rios and coworkers.[35]

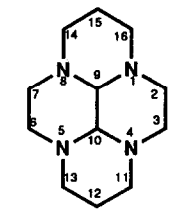
Table 7 Relative energies (kcal/mol) of 1,4,5,8- tetraazadecalin (TAD) derivatives, as calculated by molecular mechanics (MM2-82 and MM2-AE)

conformations on N 1 4 5 8	MM2	MM2-AE	MM2	MM2-AE	MM2	MM2-AE
	trans-TAD		trans-1,5-DMTAD[c]			
eq eq eq eq	2.1	6.6	1.9	6.5		
eq ax eq ax	0.3	4.9	0.0	7.0		
ax ax ax ax	3.2	>10				
eq eq ax ax	0.1	5.0				
ax eq eq eq	1.4	4.0				
	cis-TAD		cis-1,5-DMTAD[c], I		cis-1,5-DMTAD[c], II	
eq eq eq eq	1.3	0.9	0.2	0.0	0.4	0.7
ax eq ax eq	2.1	1.6				
eq ax eq ax	1.2	6.6	1.5	1.8	0.1	7.3
ax ax eq eq	0.0	2.3				
ax eq eq eq	0.7	0.0				
ax ax ax ax	3.5	>10				
	trans-2,6-DMTAD[b]		trans-1,4,5,8-TMTAD[3,4]			
eq eq eq eq	2.2	5.7	>10.	>10.		
eq ax eq ax	0.3	4.0	1.5	0 3		
	cis-2,6-DMTAD[b]		cis-1,4,5,8-TMTAD[3,4]			
eq eq eq eq	1.4	0.0	3.1	0.3		
ax eq ax eq	1.4	0.7				
eq ax eq ax	2.1	5.9	0.0	0.0		
ax ax eq eq	0.0	1.5	6.3	2.8		
	trans-2,2,6,6-TMTAD		trans-1,8-BTAD			
eq eq eq eq	2.0	5.7	0.6	4.8		
eq ax eq ax	0.0	4.0				
eq eq eq ax			0.0	4.3		
ax eq ax eq	0.8	3.8				
eq eq ax ax	0.3	3.6	2.3	4.7		
	cis-2,2,6,6-TMTAD		cis-1,8-BTAD			
eq eq eq eq	1.0	0.0	1.2	0.5		
eq eq ax eq			1.2	3.4		
ax eq ax eq	1.6	0.3				
eq eq eq ax			1.0	0.0		
eq ax eq ax	1.9	5.6				
eq eq ax ax	0 2	1 2	2 4	5 1		

a) DM = dimethyl; TM = tetramethyl; B = bridged (1',3'-propylidene); for numbering and conformation, see Scheme 1.
b) Energies of 2,7-DMTAD are similar within ca. 0.1 kcal/mol.
c) cf. Scheme 5.

The data of the calculated TAD systems are given in Table 7. For good measure we also performed the calculations with the original MM2(82) version. Rios and coworkers have recently used MM2(80) to calculate some small N-C-N molecules[36] as well as some large systems,[37] including TAD and its 1,4,5,8-tetramethyl derivatives. Using these and some of

their more detailed and unpublished results (kindly supplied by Prof. Rios) on the above two systems, we were able to compare geometrical parameters and steric energies from their calculations and our own MM2-82 results (Table 7) and found them all but identical. However, the calculated structural parameters of these two and all the other molecules can not be compared with experimental data, since none are available. Hence they are not tabulated here along with the relative energies;[38] to be sure, only those obtained by MM2-AE exhibit the bond lengthening of axial C-N bonds and shortening of equatorial ones, as expected for a weak anomeric effect.[4] As to the relative energies (Table 7), they are difficult to compare with the experimental results of this study, since the latter were obtained in polar, often protic media, which should strongly influence the behaviour of these systems (almost all of which are hardly soluble in non-polar solvents). Thus, TAD is found by both methods to be most stable in the *cis* form (although MM2-82 provides also appreciable *trans* components), while it could be measured only in water, where the *trans* isomer prevails and it is the only one in solid form. In the 2,6-DMTAD manifold, we have observed only the *trans* forms (t_{ee} t_{ea}), while the *cis* is calculated to be more stable by both methods, each with a different N-H conformation. For the 2,2,6,6-TMTAD system, the *trans* form is again the only observed one; this time, MM2 prefers the *trans* isomer while MM2-AE the *cis* form with its stereoelectronic favourable conformations. Similar discrepancies are seen also in the 1,5-DMTAD and 1,8-BTAD and are attributed to the highly polar molecules and experimental conditions. For the 1,4,5,8-tetramethyl derivatives (TMTAD), however, MM2-AE gives a more balanced picture, in accord with experiment.[3] It appears that the unsubstituted NH groups in TAD compounds are highly sensitive chemical centers in solution and may distort the conformational behaviour of the latter.



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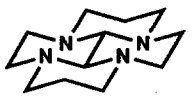
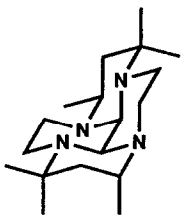
cis



trans



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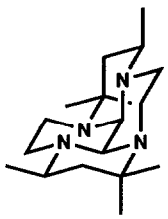

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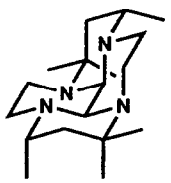

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To conclude our computational effort in this study, and in view of the above described results (Table 7) and tribulations, we wanted further data to assess the viability of our computational method. Hence, we sought to calculate TAD systems with known structures and geometrical parameters, from X-ray diffraction analyses. The natural candidates for such calculations were compound **10** and his all-equatorial isomer, the X-ray diffraction analyses of which had been reported.[10] The data (atomic coordinates, etc.) were, however, not included in the original papers[10] and neither could we locate them in the Cambridge Structural Database (although the entries exist). There are, however, a number of additional such doubly annelated TAD compounds in the crystallographic literature, of various substitution and configuration (albeit most of them *cis*), namely, in the (1,8)(4,5)-bis(1',3'-propylidene)-1,4,5,8-tetraazadecalin (**12**) series.[39-43] In fact, we had already performed calculations[4] of two such doubly bridged TAD derivatives (**13** and **14**) and found quite good agreement between the observed[39] and (MM2-AE) calculated geometrical parameters (bond lengths and bond angles) of the anomeric moiety.

Table 8 Structural data: bond lengths (r, angstrom) and bond angles (θ, deg.) within the C-N-C-N-C moieties of *cis*- and *trans*-(1,8)(4,5)-bis(1',3'-propylidene)-1,4,5,8-tetraazadecalin (**12** c,t) and its 11,11,13,14,14,16-hexamethyl-derivatives (**14** and **15**), as calculated by MM2-AE vs. experimental (X-ray diffraction) results.[40-42]

	12c		**12t**		**14**		**15**	
	X-RAY[40]	MM2-AE	X-RAY[40]	MM2-AE	X-RAY[41]	MM2-AE	X-RAY[42]	MM2-AE
ANOMERIC CENTERS C2-N1-C9-N8-C7								
r								
C2-N1	1.437(6)	1.465	1.463(6)	1.464	1.471(9)	1.465	1.473(6)	1.466
N1-C9	1.471(5)	1.459	1.461(6)	1.451	1.477(7)	1.462	1.487(4)	1.465
C9-N8	1.461(6)	1.446	1.470(5)	1.451	1.466(8)	1.452	1.449(5)	1.448
N8-C7	1.469(7)	1.464	1.469(5)	1.464	1.485(7)	1.466	1.464(5)	1.465
θ								
C2-N1-C9	109.8(3)	110.5	109.2(3)	110.9	109.1(5)	109.6	110.4(3)	110.0
N1-C9-N8	111.7(3)	113.3	109.3(3)	111.0	112.6(5)	113.5	112.4(3)	113.5
C7-N8-C9	111.9(3)	112.7	108.8(3)	110.8	109.5(5)	110.8	111.5(2)	111.9
ANOMERIC CENTERS C3-N4-C10-N5-C6								
r								
C3-N4	1.469(7)	1.464	1.469(5)	1.464	1.466(8)	1.466	1.471(5)	1.466
N4-C10	1.461(6)	1.446	1.470(5)	1.451	1.467(9)	1.452	1.453(5)	1.448
C10-N5	1.471(5)	1.459	1.461(6)	1.451	1.473(7)	1.462	1.471(5)	1.465
N5-C6	1.437(6)	1.465	1.463(6)	1.464	1.459(9)	1.465	1.469(6)	1.466
θ								
C3-N4-C10	111.9(3)	112.7	108.8(3)	110.9	109.5(5)	110.8	110.5(3)	111.9
N4-C10-N5	111.7(3)	113.3	109.3(3)	111.0	112.6(5)	113.5	113.3(2)	113.5
C6-N5-C10	109.8(3)	110.5	109.2(3)	110.9	107.6(5)	109.6	110.3(2)	110.0

We proceeded, therefore, to calculate these other highly substituted TAD compounds for which X-ray analytical data are available.[40-42] The calculated vs. experimental structural parameters in the anomeric moieties[38] are assembled in Table 8 for the unsubstituted isomers (**12c,t**) and the hexamethyl substituted *cis* derivatives (**14** and **15**). In the previous calculation and comparison of results for compound **14**[4] we had to recalculate the geometrical parameters from the atomic coordinates reported[39]; another, subsequent analysis of the same compound (**14**) gave a new set of parameters, which we used here. The agreement between the calculated and experimental geometries is good, in particular concerning the C-N-C and N-C-N bond angles and the trends in the NC-N bond lengths in all *cis* compounds (i.e., bond shortening in equatorial and bond lengthening in axial C-N bonds), although they appear to be consistently shorter by ca. 0.01 Å. It is planned to look into this problem presently.

In conclusion, we have presented a fairly comprehensive study of 1,4,5,8-tetraazadecalin and a variety of its peripherally and N-substituted derivatives. Their different configurations, static and dynamic chemical and conformational behaviour (assignment and isomerization pathways) have been examined using a variety of ^{1}H-, ^{13}C- and ^{15}N-NMR techniques. Thermodynamic and kinetic parameters were extracted and the stereoelectronic effect in the N-C-N moiety was evaluated, also using molecular mechanics calculations with the MM2-AE force field, as previously parameterized for these purposes. The information thus obtained will be of appreciable significance in studies toward the construction of new ion-coordination and inclusion compounds, now in course.

Experimental Section

All known TAD compounds (**1-8**) were prepared according to ref. 2. Isomerization and equilibration were performed in NMR tubes during or prior to measurement. 1,8-(1',3'-propylidene)-*trans*- and *cis*-1,4,5,8-tetraazadecalin (**8t** and **8c**) were resolved by fractional crystallisation form ethanol/water: **8t** was isolated in pure form but **8c** only in an enriched (ca 80%) mixture. The mother liquor deposited on standing (ca. one month) crystals of **9c**.

^{1}H and ^{13}C-NMR spectra were measured on spectrometers Bruker AM-360-WB (Tel-Aviv, 360 MHz for ^{1}H and 90.5 MHz for ^{13}C) and AM-400-WB (Zürich, 100.6 MHz for ^{13}C). ^{15}N-NMR spectra were measured on the AM-400-WB spectrometer at 40.6 MHz using a 10 mm broad-band probe-head. Chemical shifts are given in ppm from TMS for ^{1}H and ^{13}C, and from $CH_3{}^{15}NO_2$ as external reference for ^{15}N. The samples were dissolved in ca. 2.5 ml of solvent in 10 mm tubes.

Because of solubility limitations only the N-alkyl-substituted tetraazadecalins (**3, 8, 10**) could be dissolved in $CDCl_3$ in an amount sufficient for the ^{15}N measurements. All other compounds (**1, 4, 5, 6, 7**) were dissolved in H_2O/D_2O. The concentrations were in the range of 0.5 to 1 M.

All ^{15}N-NMR spectra were recorded at natural isotope abundance, in most cases without proton decoupling. The pulse angle was 30° and during the relaxation delay of 4 s the decoupler was switched off. Typical measurement time was 10-12 h. Due to the low amount of material available (85 mg, M_r = 402) $Cr(acac)_3$ was added to the $CDCl_3$ solution of **10** in a concentration of 0.1 M. For the measurement of the proton-detected ^{1}H,^{13}C-heterocorrelated spectrum of **10** a sample of 5 mg in 0.5 ml $CDCl_3$ in a 5mm tube was employed.

Acknowledgments

We are grateful to Dr. R. W. Turner for a sample of compound **10**. The calculations were performed on a CYBER 170/990 computer at the Computational Center of Tel-Aviv University. We thank Dr. Hanoch Senderowitz for help with some calculations, Mrs. Sarah Weinman for technical assistance and Prof. Uri Shmueli and Prof. Israel Goldberg for crystallographical advice. This work has been supported by the Swiss National Science Foundation (to the Zürich group).

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