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STRUCTURE AND CONFORMATION OF HETEROCYCLES—12[1]

1,4,5,8-TETRAACYL-1,4,5,8-TETRAAZADECALINS: CONFIGURATIONAL AND CONFORMATIONAL ANALYSIS IN THE CRYSTAL AND IN SOLUTION

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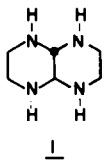
Abstract—A series of 1,4,5,8-tetraacyl-1,4,5,8-tetraazadecalins was studied and found to exist in *trans* form in analogy with the parent system.[2] Only tetraacetyltetraazadecalin (TATAD) could be obtained in both *trans* and *cis* forms, which were investigated in detail by X-ray diffraction analysis and NMR techniques. *trans*-TATAD (**8**) occurs in the crystal in a centrosymmetric double twist-boat conformation whereas *cis*-TATAD (**9**) has one ring as a flattened chair and the other as a twist boat with all the amide CO's syn-oriented. Three out of seven possible rotameric forms of **9** occur at low temperature in solution. The free energy of activation of amide rotation *in trans*-TATAD (**8**) is 14.5 kcal/mol, in contrast to *ca* 12 kcal/mol in the unique *cis* isomer (**9**).

In continuation of our studies on 1,4,5,8-tetraazadecalins, we were interested to see how the conformation of the system is affected by imparting the nitrogens (partial) trigonal character. It should be pointed out that 1,4,5,8-tetrazadecalin (TAD) itself and a number of its susbstitued derivatives have been shown to exist in solution in double chair conformations with *trans* configuration (**1**).[2] It may also be worth recalling that various 1,4-diacyl-piperazines (i.al. **2** and **3**) had been studied in solution[3] as well as in crystals[4] (e.g. **3**, **4**) and found to occur in flattened chair conformations, with a recent exception namely *cis*-2,5-dimethyl-1,4-dibenzoylpiperazine (**5**) which was found[5] to exist in twist-boat conformation. The latter is often encountered in 6-membered rings with sp^2 centers in 1,4-positions (e.g. 1,4-cyclohexanedione).[6]



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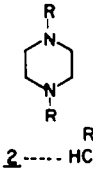
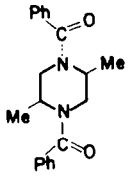


2 ----- HCO
3 ----- MeCO
4 ----- PhCO



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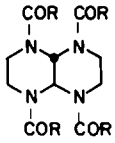
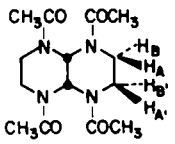


6 ------ Ph
7 ------ OEt
8 ------ Me



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RESULTS AND DISCUSSION

Synthesis and characterization in solution. The reaction of TAD (**1**) with appropriate acid chlorides namely, benzoylchloride, ethyl chloroformate and acetyl chloride led to one tetraacylated product in each case, namely the 1,4,5,8-tetrabenzoyl-(**6**), tetracarboethoxy-(**7**) and tetraacetyl-(**8**) derivatives, which were assigned *trans* geometry, on the strength of the known starting materials (**1**) configuration.[2,8]

When however, TAD (**1**) was treated with acetic anhydride, the reaction was much slower and we isolated, in addition to **8**, a second 1,4,5,8-tetraacetyl-1,4,5,8-tetraazadecalin (TATAD) isomer which was hence tentatively assigned the *cis* configuration (**9**). No thermal or acid catalysed interconversion between **8** and **9** could be observed.

The above assignments gained in strength from ^{13}C-satellite ^1H NMR spectroscopic measurements of the angular protons in these compounds. Thus we found for $^3J_{9,10}$: 10.5 Hz in **7** and 10.0 Hz in **8** and 6.2 Hz in **9**. These values for **7** and **8** constitute clear indication that the respective compounds possess *trans* configuration (i.e. $^3J^{trans}_{9,10} = {}^3J_{ax,ax}$) but the value for **9** is considerably higher than expected (for $^3J^{cis}_{9,10} = {}^3J_{eq,ax} = 2$–3 Hz)[2], providing a first hint that we may deal with non-chair conformations of *cis*-TATAD.

In continuation, we performed an analysis of the AA'BB' NMR spectral pattern of the peripheral 4-proton system in *cis*-TATAD (**9**) using the PANIC adaptation (ASPECT 2000) of the LAOCN 3 pro-

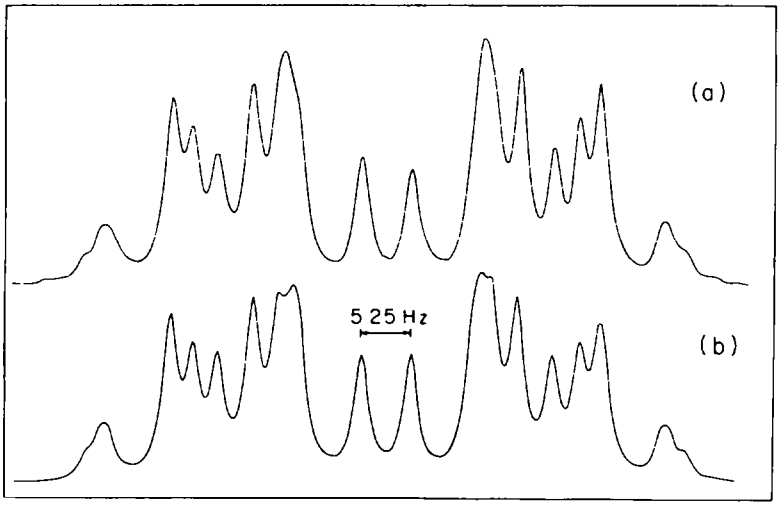

Fig. 1. 90 MHz ^{1}H-NMR spectrum of the peripheral (P) CH_2–CH_2 grouping of *cis*-TATAD (**9**) in $CDCl_3$ (37°): (a) experimental-and (b) simulated (PANIC) scan.

gram.[4] The coupling constants which emerged from the simulated *vs* observed spectra (Fig. 1, data at 90 MHz): $^2J^{gem}_{AB(A'B')} = -13.49$, $^3J^{cis}_{AA'} = 5.73$, $^3J^{cis}_{BB'} = 4.66$, $^3J^{trans}_{AB'} = {}^3J^{trans}_{A'B} = 6.95$ Hz led to a value of $R = \frac{J_{trans}}{J_{cis}} = 1.34$. The above measurements were checked for reliability at 200 MHz and similar results were obtained indicating the occurrence of a twist-boat conformation.[9]

To put these assignments and our conclusions therefrom on a firm and unequivocal basis and to be able to probe into the detailed structural parameters of these systems, we decided to perform X-ray diffraction analyses of some representative compounds. We started with tetracarboethoxy-1,4,5,8-tetraazadecalin (TCTAD; **7**) since we needed it also for chemical correlation work of some importance.[1] While the *trans*-double twist-boat structure (Fig. 2) emerged quite readily, we were somewhat disturbed

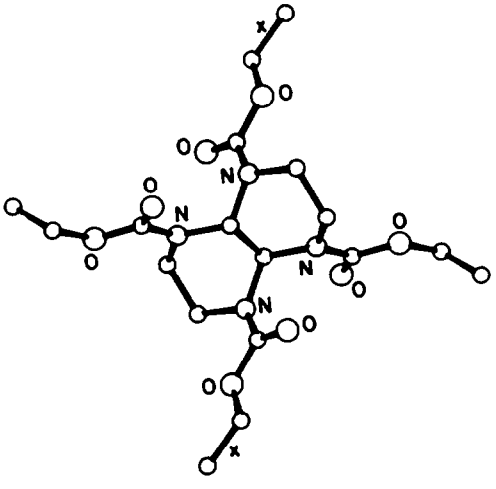

Fig. 2. X-ray structure of *trans*-1,4,5,8-tetracarboethoxy-1,4,5,8-tetraazadecalin (**6**). The "X" marked ethyl groups are probably disordered.

by the rather high thermal motion found in the Et groups which led to low accuracy and hence further crystallographic work on *trans*-TCTAD was discontinued. The two 1,4,5,8-tetraacetyl-1,4,5,8-tetraaza decalin (TATAD) derivatives (**8** and **9**), however, lent themselves to accurate analysis.

X-ray crystallographic work

Experimental and structure determination. Well-developed colourless crystals of **8** and **9** were subjected to the X-ray investigation which was carried out with the aid of a CAD4F diffractometer system and the Tel Aviv University Computational facilities. Some important crystal data and other pertinent parameters and results of the X-ray study are summarized in Table 1.

In each case, the unit cell dimensions were determined from a least squares fit of 25 carefully centered reflections. The diffraction symmetry showed both crystals to be monoclinic and the space groups were readily indicated by systematic absences. Since the crystals of **8** contain only two molecules in a unit cell of $P2_1/c$, it was almost obvious that **8** is, in fact *trans*-TATAD. Intensity data collection from **8** and **9** was performed in the angular range: $1° \leqslant \theta \leqslant 27°$, using graphite-mono-chromatized molybdenum radiation and the $\theta/2\theta$ scan technique. In each of the two experiments, three reflections were monitored at 1 hr intervals and their intensities indicate good stability of crystals and apparatus. The intensity data were converted to structure amplitudes without absorption and extinction corrections, and the latter were reduced to independent data sets in the usual manner. Only reflections with positive net intensities were used at any stage, and reflections with $I < 3\sigma$ were considered as unobserved.

Both structures were determined by direct methods with the aid of the MULTAN 78[10] system. Least squares refinements of the above two trial structures proceeded smoothly through the usual isotropic and anisotropic stages, to R values (for observed reflections) of 0.038 and 0.041 for *cis*-TATAD and

Table 1. Summary of the X-ray analysis

	cis-TATAD	trans-TATAD
Cell data:		
a (Å)	8.919(2)	8.106(2)
b (Å)	15.157(3)	11.115(2)
c (Å)	11.253(2)	8.593(2)
β (°)	91.88(2)	104.53(1)
Space group	$P2_1/n$, Z=4	$P2_1/c$, Z=2
Crystal size (mm)	0.3x0.4x0.5	0.2x0.3x0.4
Scan speed (deg. min^{-1})	0.91 - 5.0	0.8 - 4.0
Scan range (ω, deg.)	1.0+0.3 tan θ	0.9+0.3 tan θ
Reflection count:		
No measured (I>0)	3197	1654
No. independent (all)	2961	1366
No. Independent*(I>3σ)	2373	955
R (I>3σ)	0.038	0.041
R(all)	0.056	0.070
No. of parameters	287	144

*excluding extinctions - see text.

trans-TADAD, respectively. All the H atoms were readily located in difference maps at the beginning of the anisotropic refinements, and were included in subsequent calculations with isotropic vibration parameters. Fourteen reflections from *cis*-TATAD were excluded from the refinements, since they exhibited probable effects of extinction. The final difference maps were found to be featureless.

Atomic scattering factors for C, N and O atoms were taken from the International Tables,[11] while those of Stewart *et al.*[12] were used for H atoms.

Fractional atomic coordinates and equivalent isotropic vibration parameters[13] of the heavy atoms are given in Table 2.†

Description of the structures. Figure 3 shows ORTEP drawings of *trans*-TATAD (**8**) and *cis*-TATAD (**9**) and the relevant bond distances and dihedral angles are given in Tables 3 and 4. The results of our analysis confirmed the *trans* configuration of **8** (Fig. 3a) showing that it consists of two fused, centrosymmetrically related twist-boats, similar to those found in the tetracarboethoxy derivative **7** (Fig. 2)[1]. Compound **9**, however, was found to exist indeed in the *cis* configuration (Fig. 3b), thus bearing out the indications based on NMR coupling constants (*vide supra*). The TAD skeleton of *cis*-TATAD (**9**) consists of an asymmetrically flattened chair fused with a twist-boat. The two crystallographically independent N-acetyl groups in *trans*-TATAD (**8**) and the four ones in *cis*-TATAD (**9**) are nearly planar, evidently due to the strong conjugation in the N-C = O systems. All six N-acetyl groups appear to be well ordered in the solid, as indicated by the small and nearly isotropic thermal parameters of the N atoms.[15] It is of interest to note that the least planar N-acetyl groups, involving N(4) in *cis*-TATAD (**9**) and N(1) in *trans*-TATAD (**8**) are associated with the longest intracyclic N–C bonds while the most planar amide groups, involving N(5) in *cis*-TATAD (**9**) and N(8) in *trans*-TATAD (**8**) have the shortest N–C bonds within the corresponding TAD systems (*cf* Table 3 and Fig. 3). Still in this context, an examination of the average value of the bond angles around each N atom in **8** reveals that only the value obtained for N(4), *viz* $\bar{\alpha}_4 = 118.3°$ is significantly lower than 120°. This slight pyramidality is associated [17] with somewhat elongated intracyclic as well as exocyclic N–C bonds (*cf* Table 3 and Fig. 3).

With regard to the conformation of the ring systems, the notable asymmetric flattening of the chair-ring in *cis*-TATAD **9** (see the dihedral angles in the opposite C–N–C sections of this ring—Fig. 3(b) and Table 4) appears to reflect the strain induced by the rather strong steric interactions present. Thus, an unusually short 1–5 contact distance O(4)---N(5) of 2.76 Å is observed, in addition to several other short contacts.‡ Interestingly, the adjacent twist-boat ring in this molecule (**9**) has practically an ideal form. The

†The crystal data, final atomic coordinates, bond length, bond angles and dihedral angles have been deposited with the Cambridge Crystallographic Data Centre. The positional and thermal atomic parameters and structure factor tables have been deposited as a Supplementary Publication (Sup. 00000,00 pages) with the British Library, Lending Division.

‡It may be noted that a 1-5 short contact of a similar nature (although in a different chemical system) has been encountered by one of us (U.S.) in the structure of a dimethylaminodicarbomethoxy acrylate.[15a]

Table 2. Final atomic coordinates and equivalent isotropic vibration parameters of the heavy atoms†

Atom	X	Y	Z	U_{eq}(Å^2)
		trans-TATAD (8)		
N(1)	.6260(2)	.0557(1)	.6970(2)	.0315
C(2)	.7614(3)	-.0368(2)	.7383(3)	.0425
C(7)	.2584(3)	.1294(2)	.3949(3)	.0380
N(8)	.3176(2)	.0727(1)	.5520(2)	.0283
C(9)	.4764(2)	.0069(2)	.5799(3)	.0283
C(1)	.6510(3)	.1736(2)	.7353(3)	.0381
O(1)	.5474(2)	.2507(1)	.6758(3)	.0603
C(1')	.8104(3)	.2061(2)	.8600(3)	.0535
C(8)	.2281(3)	.0866(2)	.6651(3)	.0360
O(8)	.0951(2)	.1430(2)	.6360(2)	.0608
C(8')	.2986(3)	.0320(2)	.8268(3)	.0485
		cis-TATAD (9)		
Atom	X	Y	Z	U_{eq}(Å^2)
N(1)	.2204(1)	.3035(1)	.5294(1)	.0366
C(2)	.3283(2)	.3246(1)	.6247(1)	.0429
C(3)	.2636(2)	.3034(1)	.7438(1)	.0512
N(4)	.1866(1)	.2176(1)	.7479(1)	.0332
N(5)	.1218(1)	.0836(1)	.6433(1)	.0297
C(6)	.2726(2)	.0459(1)	.6547(1)	.0367
C(7)	.3867(2)	.1076(1)	.6019(1)	.0353
N(8)	.3180(1)	.1562(1)	.5011(1)	.0308
C(9)	.1856(1)	.2097(1)	.5245(1)	.0287
C(10)	.1139(1)	.1791(1)	.6400(1)	.0269
C(1)	.1497(2)	.3618(1)	.4545(2)	.0466
O(1)	.0514(2)	.3379(1)	.3836(1)	.0659
C(1')	.1976(3)	.4569(1)	.4618(2)	.0686
C(4)	.1305(2)	.1915(1)	.8548(1)	.0398
O(4)	.0258(1)	.1406(1)	.8607(1)	.0554
C(4')	.2057(2)	.2275(1)	.9664(1)	.0596
C(5)	.0016(2)	.0292(1)	.6491(1)	.0354
O(5)	.0204(1)	-.0505(1)	.6610(1)	.0565
C(5')	-.1534(2)	.0669(1)	.6361(1)	.0442
C(8)	.3659(2)	.1405(1)	.3890(1)	.0353
O(8)	.4738(1)	.0932(1)	.3726(1)	.0545
C(8')	.2813(2)	.1818(1)	.2863(1)	.0464

† X, Y and Z are fractional coordinates and Ueq is one third of the trace of the atomic anisotropic vibration tensor, after transformation to a cartesian system[13]. The parameters of the H atoms are included in the deposited material.

two (equivalent) twist-boats in *trans*-TATAD (**8**) are, however, rather distorted. In any case, it appears that most of the N-acyl piperazine systems that have been worked out were found to adopt preferentially the twist-boat conformation.

No unreasonably short intermolecular contacts have been observed. Consideration of the above elaborated structural features suggests that we deal with rather rigid structures and this is in fact borne out by the analyses of the anisotropic vibration tensors in terms of the rigid-body motion tensors TLS.[18] Such analyses were performed and their short summary is presented in Table 7. Of particular interest is the fact that the TAD nuclei of *cis*-TATAD and *trans*-TATAD are the most rigid fragments, in spite of the fact that they contain single bonds only. It thus appears, that the tetraacetyl substitution has most effectively "locked" the molecular frameworks of *cis*-TATAD and their conformations seem to be determined by an interplay of strong conjugation and significant non-bonded interactions.

Variable temperature ^{13}C-NMR *work*

Following the conformational analysis of *cis*. and *trans*-TATAD (**8** and **9**) in the crystal, their study in solution was imperative. Hence we undertook a variable temperature NMR spectroscopic investigation. In this framework the *trans* isomer **8** was less amenable to low temperature work because of its low solubility but the study of the *cis* isomer **9** (anyway the more interesting one) was rewarding.

The ^{13}C-NMR spectra of **9** at + 30° and − 70° (in MeOH-d_4) are depicted in Fig. 4 and the spectrum at − 70° is given in Fig. 5, showing each group of

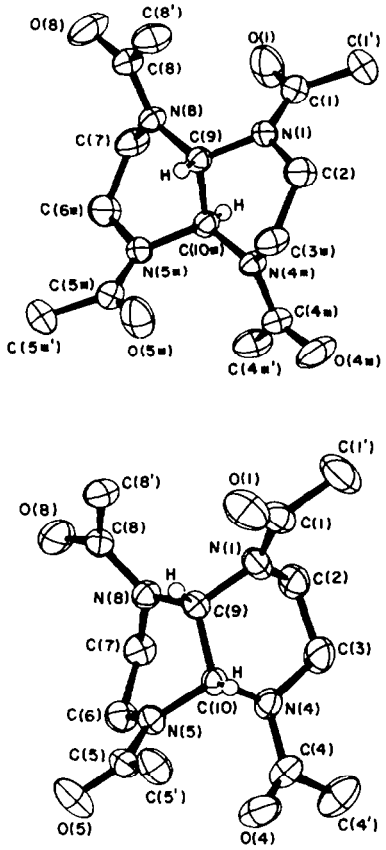

Fig. 3. X-ray structures of the isomeric 1,4,5,8-tetra-acetyl-1,4,5,8-tetraazadecalins: (a) *trans*-TATAD (**8**) and (b) *cis*-TATAD (**9**). The atoms denoted by asterisks are related by inversion to the part of *trans*-TATAD given in Table 2. The same applies to corresponding atomic symbols in Tables 2–5.

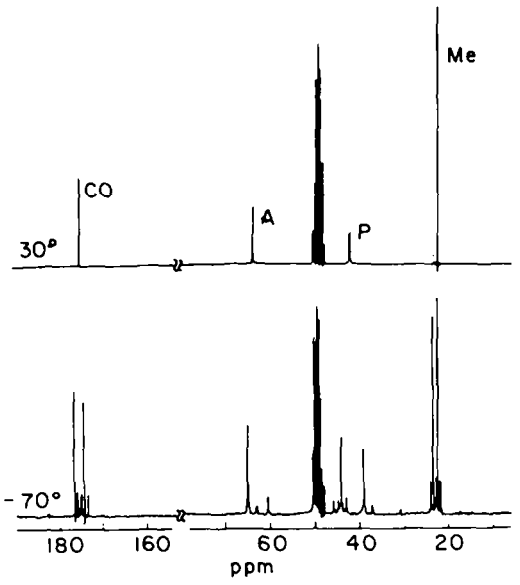

Fig. 4. 50.4 MHz ^{13}C-NMR spectra of *cis*-TATAD (**9**) 30° and −70°: Me = methyl, P = peripheric, A = angular and CO = carbonyl ^{13}C resonances.

resonances *viz* of the Me, peripheral (P), angular (A) and CO ^{13}C nuclei. The sequences of low temperature Me, P, A and CO ^{13}C-NMR spectra were all measured and one of those (Me) is depicted in Fig. 6.

Careful examination of Figs. 4 and 5 reveals that the homogeneous species at room temperature (where fast amide rotation and ring inversion take place) transform at −70° into a mixture of three distinct species I, II and III (Table 6) taken to be different amide rotamers in ratio of *ca* 6:3:1, respectively). Following the variable temperature ^{13}C-NMR spectral behaviour of the various groups as exemplified in

Table 3. Bond distances and their e.s.d.

	trans-TATAD (8)		
N(1) - C(2)	1.481(3)	N(1) - C(9)	1.471(2)
N(1) - C(1)	1.354(3)	C(2) - C(3*)	1.518(3)
C(7) - N(8)	1.458(3)	N(8) - C(9)	1.447(2)
N(8) - C(8)	1.360(3)	C(9) - C(10*)	1.523(3)
C(1) - O(1)	1.219(3)	C(1) - C(1')	1.501(3)
C(8) - O(8)	1.218(3)	C(8) - C(8')	1.492(3)
	cis-TATAD (9)		
N(1) - C(2)	1.453(2)	N(1) - C(9)	1.457(2)
N(1) - C(1)	1.361(2)	C(2) - C(3)	1.511(2)
C(3) - N(4)	1.472(2)	N(4) - C(10)	1.478(2)
N(4) - C(4)	1.376(2)	N(5) - C(6)	1.464(2)
N(5) - C(10)	1.449(2)	N(5) - C(5)	1.356(2)
C(6) - C(7)	1.517(2)	C(7) - N(8)	1.469(2)
N(8) - C(9)	1.464(2)	N(8) - C(8)	1.365(2)
C(9) - C(10)	1.539(2)	C(4) - C(4')	1.506(2)
C(4) - O(4)	1.214(2)	C(5) - C(5')	1.499(2)
C(5) - O(5)	1.226(2)	C(8) - C(8')	1.497(2)
C(8) - O(8)	1.219(2)	C(1) - C(1')	1.505(2)
C(1) - O(1)	1.221(2)		

Table 4. Dihedral angles and their e.s.d.

trans-TATAD (8)							
N(1)	-C(2)	-C(3*)	-N(4*)	36.7(3)	C(6*)	-C(7)	-N(8) -C(9) 57.3(2)
C(7)	-N(8)	-C(9)	-C(10*)	-11.5(2)	N(8)	-C(9)	-C(10*) -N(5*) -50.9(2)
C(10*)	-C(9)	-N(1)	-C(2)	-70.6(2)	C(9)	-N(1)	-C(2) -C(3*) 23.9(3)
N(1)	-C(9)	-N(8)	-C(7)	111.3(2)	C(2)	-N(1)	-C(9) -N(8) -166.2(2)
C(1')	-C(1)	-N(1)	-C(2)	-15.7(4)	C(1')	-C(1)	-N(1) -C(9) 179.0(2)
C(8')	-C(8)	-N(8)	-C(9)	0.6(3)	C(8')	-C(8)	-N(8) -C(7) -176.9(2)
O(1)	-C(1)	-N(1)	-C(2)	166.5(2)	O(1)	-C(1)	-N(1) -C(9) 1.1(4)
O(8)	-C(8)	-N(8)	-C(7)	2.4(3)	O(8)	-C(8)	-N(8) -C(9) 179.9(2)
C(1)	-N(1)	-C(2)	-C(3*)	-143.3(2)	C(1)	-N(1)	-C(9) -C(10*) 96.4(2)
C(1)	-N(1)	-C(9)	-N(8)	-26.8(3)	C(8)	-N(8)	-C(9) -C(10*) 170.9(2)
C(8)	-N(8)	-C(7)	-C(6*)	-125.0(2)	C(8)	-N(8)	-C(9) -N(1) -66.3(3)
cis-TATAD (9)							
N(1)	-C(2)	-C(3)	-N(4)	44.6(2)	C(2)	-C(3)	-N(4) -C(10) -28.8(2)
C(3)	-N(4)	-C(10)	-C(9)	27.1(2)	N(4)	-C(10)	-C(9) -N(1) -41.5(1)
C(10)	-C(9)	-N(1)	-C(2)	61.8(1)	C(9)	-N(1)	-C(2) -C(3) -63.2(2)
N(8)	-C(9)	-C(10)	-N(5)	-39.4(1)	C(9)	-C(10)	-N(5) -C(6) 66.2(1)
C(10)	-N(5)	-C(6)	-C(7)	-27.7(2)	N(5)	-C(6)	-C(7) -N(8) -32.4(1)
C(6)	-C(7)	-N(8)	-C(9)	58.1(1)	C(7)	-N(8)	-C(9) -C(10) -19.5(1)
N(1)	-C(9)	-C(10)	-N(5)	-164.1(1)	N(8)	-C(9)	-C(10) -N(4) 83.1(1)
N(1)	-C(9)	-N(8)	-C(7)	104.4(1)	C(2)	-N(1)	-C(9) -N(8) -61.8(1)
C(3)	-N(4)	-C(10)	-N(5)	147.8(1)	N(4)	-C(10)	-N(5) -C(6) -57.8(1)
C(1)	-N(1)	-C(2)	-C(3)	113.4(2)	C(1)	-N(1)	-C(9) -C(10) -115.0(1)
C(1)	-N(1)	-C(9)	-N(8)	121.5(1)	C(8)	-N(8)	-C(9) -N(1) -84.8(1)
C(8)	-N(8)	-C(9)	-C(10)	151.3(1)	C(8)	-N(8)	-C(7) -C(6) -113.0(1)
C(5)	-N(5)	-C(10)	-C(9)	-121.0(1)	C(5)	-N(5)	-C(10) -N(4) 115.1(1)
C(5)	-N(5)	-C(6)	-C(7)	159.0(1)	C(4)	-N(4)	-C(3) -C(2) 177.1(1)
C(4)	-N(4)	-C(10)	-C(9)	-178.5(1)	C(4)	-N(4)	-C(10) -N(5) -57.8(1)
O(1)	-C(1)	-N(1)	-C(2)	-173.8(2)	O(1)	-C(1)	-N(1) -C(9) 2.5(2)
O(8)	-C(8)	-N(8)	-C(9)	-177.5(1)	O(8)	-C(8)	-N(8) -C(7) -6.9(2)
O(5)	-C(5)	-N(5)	-C(10)	-174.2(1)	O(5)	-C(5)	-N(5) -C(6) -1.6(2)
O(4)	-C(4)	-N(4)	-C(3)	154.3(2)	O(4)	-C(4)	-N(4) -C(10) -1.0(2)
C(1')	-C(1)	-N(1)	-C(2)	6.5(2)	C(1')	-C(1)	-N(1) -C(9) -177.2(1)
C(8')	-C(8)	-N(8)	-C(9)	1.6(2)	C(8')	-C(8)	-N(8) -C(7) 172.2(1)
C(5')	-C(5)	-N(5)	-C(6)	-179.2(1)	C(5')	-C(5)	-N(5) -C(10) 8.1(2)
C(4')	-C(4)	-N(4)	-C(3)	-26.6(2)	C(4')	-C(4)	-N(4) -C(10) 178.1(1)

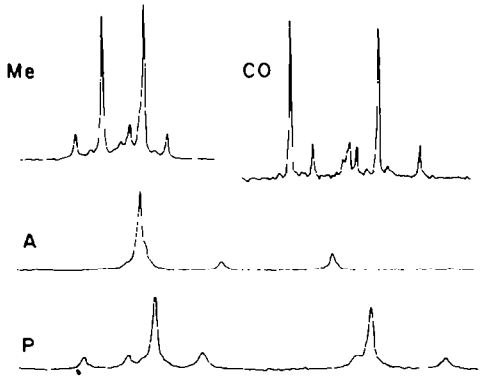

Fig. 5. Details of − 70° ^{13}C-NMR spectrum of *cis*-TATAD (**9**) in methanol-d_4.

Fig. 6 for the amide Me substituent, one can readily observe the splitting-off process of the corresponding singlets. Since we deal with unequal populations at low temperature, approximate but reliable evaluations of the coalescence points could be made in the above spectral sequences using the data of the major component I only, wherefrom the free energy of activation for the amide rotation could be independently extracted (using the expressions $k = \pi \cdot \Delta\delta/\sqrt{2}$ and $\Delta G_c^{\neq} = 4.57\, T_c\,(10.2 + \log T_c/k)$. Thus (Table 8), at around − 20°, $\Delta G^{\neq} = 12$ kcal/mol.

At this point, we are able to and should start our interpretative discussion. The X-ray diffraction study of *cis*-TATAD (**9**) has proven its configuration and provided its conformation in the crystal (Fig. 3b). The somewhat surprising feature of molecular asymmetry could be rationalized by invoking strain relief from intramolecular, mostly non-bonding interactions (*vide supra*). The conformational problem in solution is, however, more intricate. We deal with a system featuring two possible dynamic processes: (i) ring inversion and (ii) amide rotation (the latter incorporates, in fact, the N inversion mode which has meaning only in case of non-planar amide groups).

Table 5. Summary of the rigid-body motion analysis

	trans-TATAD (8)		cis-TATAD (9)	
	all [b]	decalin [c]	all [b]	decalin [c]
	3.79°	4.09°	3.74°	4.48°
L	3.27°	2.63°.	2.69°	2.71°
	1.98°	0.83°	2.52°	2.07°
	.179 Å	.172 Å	.176 Å	.172 Å
T	.162 Å	.165 Å	.161 Å	.158 Å
	.150 Å	.150 Å	.160 Å	.155 Å
ΔU[d]	.0075 Å^2	.0027 Å^2	.0058 Å^2	.0020 Å^2
$\langle\sigma^2\rangle^{1/2}$	.0010 Å^2		.0006 Å^2	

a) The r.m.s. amplitudes of librational and translational motion of trans-TATAD and cis-TATAD are calculated from the eigenvalues of the libration (L) and translation (T) tensors of these molecules and their tetraazedecalin fragments. The conventional discrepancies of the analyses (ΔU) are compared with the r.m.s. estimated standard deviations of the thermal parameters for the two structures. The effect of internal vibrations in the acetyl fragments is evident from the ΔU values for the non-H fragments of the molecules.

b) All non-H atoms

c) Tetraazadecalin fragment only

d) The r.m.s. discrepancy is given by

$$\Delta U = [\Sigma (U_{obs} - U_{calc})^2/(n-m)]^{1/2}$$

where n is the number of observational equations and m is the number of rigid body parameters [18].

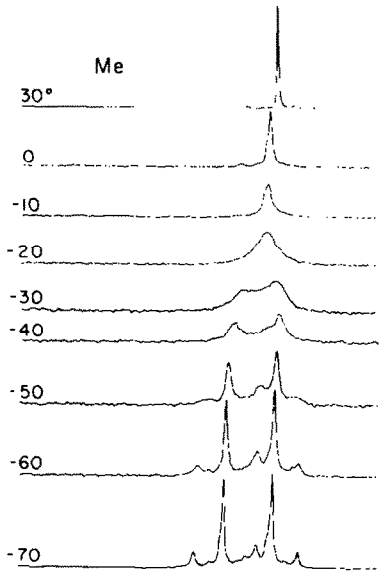

Fig. 6. Variable temperature ^{13}C-NMR spectral behaviour of the methyl (Me) groups in *cis*-TATAD (9).

Energetically, the first mode is bound to exhibit the lowest barriers, in particular since the earlier mentioned R value[9] (supported by the solid state conformation—Fig. 3b) indicates the occurrence of twist-boat conformations. The latter should then exhibit ring-inversion barriers around 6 kcal/mole[6] as opposed to the relatively high amide rotation barrier;[19] thus acetamides exhibit rotation barriers amounting to *ca* 15–20 kcal/mol.[19,20] Qualitatively, then, we can assert that in the case of *cis*-TATAD (9) in solution, it is the amide rotation that we scrutinize in our analysis.

It remains now to rationalize the rather low rotation barrier of *ca* 12 kcal/mol (Table 6) and this is readily accomplished by invoking pseudoallylic steric interaction which is well known to raise the ground state and, hence, lower the rotation barriers of appropriately N-substituted amides[21–23] (this had been labeled "$A^{(1,3)}$ strain" in the earlier literature[21,22]). Recently,[23] this concept received forceful support from the results of dynamic NMR analysis of hindered piperidyl-amides. Thus the N-acetyl derivatives of *cis*-2,6-dimethyl–and 2,2,6,6-tetramethylpiperidine exhibit ΔG^* values of 13.8 and 6.7 kcal/mol respectively as compared to 15.3 kcal/mol for the 2-Me derivative. Still, our value of 12 kcal/mol for **9** is low by these standards; we attribute this to the additional strain in the ground state due mainly to non-bonded interactions within the *cis*-tetraazadecalin structure along with the peri-interactions. Whether there is also a *trans*-annular electronic effect between the 1,4-acetamide groups contributing to the observed lowering of the barrier,[24] is difficult to assess at this stage. These last two aspects are being examined on

Table 6. Low-temperature NMR spectra of *cis*-TATAD (9) and data therefrom

Isomers[a] / Groups[b]	I	II	III	T_c, °K[d]	k_c^{rot}	$\Delta G_c^{\neq}$ kcal/mol
	^{13}C-resonances (separation in ppm)[c]					
A	1	2(4.40)	1			
P	2(5.00)	4(1.07;5.70)	2(3.70)	263	560	11.90
Me[e]	2(1.00)	4(1.03;0.63)	2(0.15)	248	112	11.95
CO	2(2.06)	4(0.87;1.50)	2(0.07)	255	230	11.94
Composition %	61	29	10			

	^{1}H-resonances and pattern[f]		g	Details
A	1	AB[j]	1	II: δ_{AB}=0.35 ppm, J_{AB}=5.5Hz[h]; III: broad(unresolved doublet?)
P	$(ABCX)_2$	ABCD + EFGH	?[k]	I: Δδ 0.08/0.28/0.94 ppm[h];
Me	2	4	2	I: Δδ = 0.19 ppm; II: Δδ = 0.12/0.2/0.24
Composition %[i]	69	20	11	

a) Resonance peak assignments were made with the aid of intensity changes induced by varying temperature and solvent polarity.[i]

b) A=angular, P= peripheral, Me = Methyl, CO = carbonyl.

c) From ^{13}C-NMR spectrum of 9 in methanol-d_4 at -70°C(50.4MHz) (Fig.4).

d) Peak coalescence temperatures for isomer I[e].

e) See also Fig. 6.

f) From ^{1}H-NMR spectrum of 9 in methanol-d_4 at -65°C (360 MHz) (Fig.7)

g) ^{1}H-NMR data of III are partly hidden. This and the fact that the H-singlet is broad and the Me-doublet exhibits unequal intensities, precludes reliable assignment.

h) Assessed using decoupling techniques.

i) The somewhat different compositions evaluated from ^{13}C- and ^{1}H-NMR spectra are attributed to concentration effects. In fact, the composition of the mixtures was also solvent dependent; thus, f.ex. in CD_3OD/CD_2Cl_2 85/15 v/v. I:II:III=50:39:11

j) The B part is appreciably more broadened than the A part. We attribute this to long-range coupling with the acetyl-Me protons in anti position.

k) Probably two AA'BB' spin systems in CD_3OD/CD_2Cl_2 20/80 v/v.

model compounds and will be reported in due course.

We turn now to the identification of the three species making up the low temperature mixture in methanol solution (Table 6). To this end, all possible rotameric forms of *cis*-TATAD (9) assuming fast ring inversion were drawn up (Table 7) along with their symmetries and hence expected NMR-spectral patterns. Comparison with the observed spectra (Table 6) allows unequivocal assignment of the major component I and some conclusive remarks on the other two. Thus, from the ^{13}C-NMR spectrum (Fig. 5 and Table 6-top), the resonances of the major component I can be extracted showing a pattern of 1:2:2:2 for the angular (A), peripheral (P), Me and CO ^{13}C nuclei, respectively. This by itself could create some ambiguity as seen from Table 7, where both 1 and 2 have such an *expected* pattern. Fortunately the ^{1}H-NMR spectrum discriminates between them by the occurrence of an $(ABCX)_2$ pattern (Fig. 7) (and *not* two different AA'BB' spectra) making 1 the compelling assignment. We are less fortunate with II (Table 6), the ^{1}H- and ^{13}C-NMR spectra of which could fit both 3 and 4 but we prefer 3 based on long range coupling arguments (Table 6, footnote j). As to III, it has a ^{13}C-NMR spectrum which certainly fits 2 (the form occurring in the crystal–*vide supra*) but the ^{1}H-NMR data are not clear enough to provide unequivocal support for it. It should be mentioned that attempts for ^{13}C chemical shifts arguments using additivity criteria were made but found too risky to use in these highly functionalized, flexible systems.

Finally, the NMR analysis of the *trans*-TATAD (8) in solution was not as successful partly because of its low solubility but mainly due to the ill-resolved peripheral ^{1}H-NMR spectrum. We succeeded however in evaluating the activation free energy for amide rotation in 8 (DMSO-d_6 solution, $T_c = 32°$, $\Delta\delta = 8.6$ Hz for the angular protons at 90 MHz) The high coalescence temperature already indicates a relatively higher barrier and indeed we calculated

Table 7. All possible amide rotameric forms of *cis*-TATAD (9), symmetries and NMR spectral patterns

Amide rotamers of cis-TATAD (9)[a]	Symmetry elements[a]	NMR: Expected spectral pattern[a,b]	Me	P	A	CO
1	C_2	^{13}C	2	2	1	2
		^1H	2	(ABCD$_2$)	1	–
2	σ_v	^{13}C	2	2	1	2
		^1H	2	2(AA'BB')[c]	1	–
3	–	^{13}C	4	4	2	4
		^1H	4	2(ABCD)[c]	AB	–
4	–	^{13}C	4	4	2	4
		^1H	4	2(ABCD)[c]	AB	–
5	C_2,σ_v,σ_v'	^{13}C	1	1	1	1
		^1H	1	(AA'BB')$_2$	1	–
6	σ_v'	^{13}C	2	2	2	2
		^1H	2	(ABCD)$_2$	AB	–
7	C_2,σ_v,σ_v'	^{13}C	1	1	1	1
		^1H	1	(AA'BB')$_2$	1	–

a) Time averaged bicyclic forms and symmetries are considered, i.e. fast ring inversion is assumed along with fixed rotameric forms, Me = methyl; P = periphery; A = angular; CO = carbonyl.

b) No accidental isochronism is considered.

c) Two different systems.

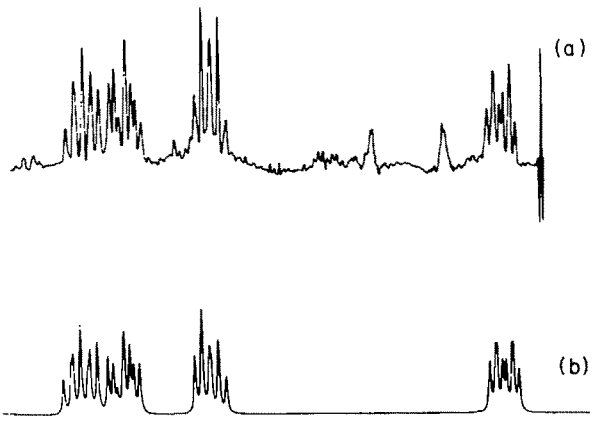

Fig. 7. 360 MHz ^{1}H-NMR spectrum of the peripheral (P) CH_2–CH_2 grouping of *cis*-TATAD (9) in methanol-d_4 at − 65°: (a) experimental- and (b) simulated (PANIC) scan.

$\Delta G^{\neq}_{305} = 14.5$ kcal/mol. This is actually a normally expected value for an α-substituted ring amide (*vide supra*) and is higher than the barrier in the *cis* isomer probably because of its extended *trans* geometry which is devoid of inter-annular interactions.

CONCLUSIONS

While most 1,4,5,8-tetraacyl-1,4,5,8-tetraazadecalins occur in *trans* configuration† similar to the parent (TAD) molecule[2], only the tetraacetyl system could be induced to give both *trans* and *cis* isomers. This is probably due to a kinetic effect, i.e. lower acylation rate allowing the formation of the *cis* isomer.

The amide groupings deeply affect the tetraazadecalin nucleus by causing appreciable strain: ring bond angles (C–N–C) increase, steric *peri* interference and pseudo-allylic ($A^{(1,3)}$) strain. The system prefers, hence, to assume twist-boat conformations and the barriers to amide rotation are high.

All the information obtained in this study, besides being of basic value, will greatly assist us in our future efforts for directed synthesis of judiciously substituted tetraazadecalins having ion inclusion capability.

EXPERIMENTAL

The X-ray diffraction experimental details are given in the text. NMR spectra were measured on Bruker 90, 200 and 360 MHz instruments. Theoretical spectra were calculated using the PANIC (ASPECT 2000) simulation programme. This was done at two or more field strengths for reliability.

The two 1,4,5,8-tetracetyl-1,4,5,8-tetraazadecalin (TATAD) isomers were prepared by adding Ac_2O to a suspension of *trans*-1,4,5,8-tetraazadecalin[2] in CCl_4. After stirring overnight at room temp the ppt was collected (84% yield) and shown (NMR) to consist of a mixture (7:2) of *cis*- and *trans*-TATAD. Resolution could be achieved by fractional crystallization from CH_2Cl_2 or MeOH.

Different yields and compositions were registered in other solvents (e.g. CH_2Cl_2–56%, *cis*:*trans* = 2:3; CH_3CN–26%, *cis*:*trans* = 10:1). Use of acetyl chloride yielded the *trans* isomer only.

Properties: *trans*-TATAD (**8**), m.p. 262 (d)°; *m/z* 310 (M^+); ν_{max} 1665 (C=O) cm^{-1}; ^{1}H-NMR δ (DMSO-d_6, 70°) 1.93 (s, 12, Me), 3.72 (bs, 8, P), 5.33 (s, 2, A); T_c^A 32°, $\Delta\delta_A = 8.6$ Hz; ^{13}C-NMR (D_2O, 90°C) 23.7 (Me), 45.2 (P), 68.7 (A), 176.3 (CO) ppm.

cis-TATAD (**9**) m.p. 214°; *m/z* 310 (M^+); ν_{max} 1665 (C=O) cm^{-1}; ^{1}H-NMR δ($CDCl_3$) 2.20 (s, 12, Me), 3.70 (m, 8, P), 5.97 (s, 2, A); ^{13}C-NMR δ($CDCl_3$) 21.7 (Me), 40.6 (P), 61.5 (A), 171.0 (CO) ppm. Simulation analysis of peripheral (P) protons in $CDCl_3$ (i) at 90 MHz and 27° (AA'BB'): $\Delta\delta_{AB} = 34.4$, $J_{AB} = -13.49$, $J_{AB'} = J_{A'B} = 6.95$, $J_{AA'} = 5.73$, $J_{BB'} = 4.66$ Hz, (ii) at 200 MHz and 50° (AA'BB'): $\Delta\sigma_{AB} = 80.58$, $J_{AB} = -13.29$, $J_{AB'} = J_{A'B} = 6.91$, $J_{AA'} = 6.04$, $J_{BB'} = 4.75$ Hz, (iii) in CD_3OD at 360 MHz and −65° (ABCX): $J_{AB} = -13.74$, $J_{CX} = -13.45$, $J_{AC} = 7.76$, $J_{BX} = 5.77$, $J_{AX} = 6.24$, $J_{BC} = 4.28$ Hz ($\delta_A = 3.930$, $\delta_B = 3.646$, $\delta_C = 3.836$, $\delta_X = 2.989$ ppm).

†An ^{1}H and ^{15}N-NMR study of the closely related *trans*-1,4,5,8-tetranitroso-1,4,5,8-tetraazadecalin has recently been published.[25]

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