Highly regioselective access to 7-substituted 1,4,7,10-tetraazacyclododecane-1-carbaldehyde derivatives: synthetic aspects and NMR elucidation of the structures. X-Ray crystal structures of 7-triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde and 7-triphenylmethyloctahydro-5*H*,9b*H*-2a,4a,7,9a- tetraazacyclo-octa[*cd*]pentalene

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7-Substituted 1,4,7,10-tetraazacyclododecane-1-carbaldehydes have been prepared through the ring opening of orthoamide protected intermediates which, in turn, were obtained by reaction of mono *N*-substituted 1.4.7,10-tetraazacyclododecane derivatives with dimethylformamide diethyl acetal. Orthoamide ring opening occurs under mild reaction conditions and is highly regiospecific. A number of mono- and bi-dimensional NMR experiments have been performed to assign unambiguously the structure of the opened compounds. The regiochemistry of such compounds has also been confirmed by elucidation of the solid-state structure of 7-triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde by X-ray crystallography. The crystal structure of 7-triphenylmethyloctahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene has also been determined.

1,4,7,10-Tetraazacyclododecane (TACD) is the basic unit for the preparation of many ligands containing additional binding sites. Recently great emphasis has been placed on the preparation of TACD derivatives containing additional carboxylate,[1] phosphonate[2] and phosphinate[3] functions. Indeed, gadolinium complexes of such ligands have proven to be useful contrast agents for magnetic resonance imaging (MRI).[4] Likewise, complexes with suitable radionuclides are under investigation for application in both radio-immunodiagnostics and -immunotherapy.[5]

Easy access to TACD by the Richman and Atkins procedure[6] has enabled the synthesis of several compounds in which the four nitrogen atoms are substituted with the same residue.†[,1]

Ligands in which one of the nitrogen atoms is substituted with a different side arm are becoming popular due to the large request for functionalized ligands for coupling to monoclonal antibodies or to organ- or tissue-specific carriers.[5] More difficult to obtain is the selective functionalization of two positions, namely 1,4 or 1,7, on the skeleton of TACD. This synthetic target is particularly challenging since it has been shown that gadolinium complexes of 1,4 and 1,7 isomeric ligands have quite different water proton relaxivities, implying different efficacies once the complexes are used *in vivo*.[9] In this study we have focused on the selective functionalization of TACD in the 1,7 positions.[10] Here we report on: (i) a general synthetic method for the preparation of 7-substituted 1,4,7,10-tetraazacyclododecane-1-carbaldehydes; (ii) NMR evidence of the regiochemistry of such compounds; (iii) X-ray crystal structures of 7-triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde and its tricyclic precursor; (iv) molecular mechanics studies related to 7-triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde.

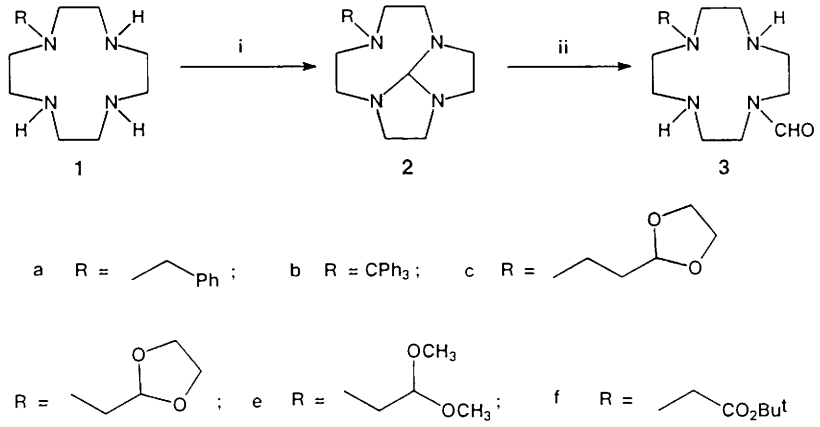
† Apart from ligands bearing acidic side arms which are used in the above mentioned applications, ligands derived from TACD with basic (*e.g.* pyrazolylmethyl and imidazolylmethyl)[7] or neutral (*e.g.* hydroxyethyl)[8] side arms have proven useful for the complexation of alkaline and transition metal cations.

Results and discussion

Synthesis

1,7-Disubstituted 1,4,7,10-tetraazacyclododecanes have already been prepared from two suitably functionalized precursors by the Richman and Atkins cyclization.[11] However, this methodology is far from optimal as many chemical functions cannot survive the harsh conditions required in the detosylation step. Alternatively, 1,7-disubstituted TACD derivatives can be obtained by condensation of a derivative of *N*-substituted iminodiacetic acid with a suitably functionalized diethylenetriamine followed by reduction of the cyclic diamide.[12] Disadvantages of this approach are the multi-step synthesis of the precursors and the low yields often reported for the cyclization.[13,14]

The macroscale preparation of TACD has already been optimized owing to the industrial interest in some of its derivatives (*e.g.* 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). Therefore, we chose TACD as a convenient building block for the synthesis of compounds **3a–f** (Scheme 1). Monoalkylation to give **1a–f** was performed in acetonitrile using a 5–10 molar excess of TACD with respect to the appropriate alkyl halide, in order to minimize the formation of polyalkylated species. The excess of TACD can easily be recovered at the end of the reaction since it largely precipitates out when the acetonitrile reaction mixture is cooled. Recently several methods have been developed for the monoalkylation of TACD that avoid the use of an excess of the parent macrocycle and take advantage of the temporary protection of three of the four nitrogen atoms.[4,15] Furthermore, Kruper *et al.* have obtained high selectivity in the monoalkylation of TACD using



Scheme 1 *Reagents and conditions:* i, $Me_2NCH(OEt)_2$, benzene, reflux, 2–4 h; ii, EtOH (THF)–H_2O

a stoichiometric amount of the alkylating agent in chloroform. Unfortunately, this procedure seems particularly successful only when the electrophile is a secondary halide.[16]

Monoalkyl derivatives **1a–f** were treated with dimethylformamide diethyl acetal in refluxing benzene to give **2a–f** in quantitative yields. Hydrolysis in ethanol–water at room temperature afforded selectively 7-substituted 1,4,7,10-tetraazacyclododecane-1-carbaldehydes **3a,c–f** in good yields (67–86%). Hydrolysis of **2b** needed to be performed in ethanol–water at reflux for 4 h and led to a 33% yield of **3b** together with some by-products. However, a noticeable improvement was obtained using tetrahydrofuran–water at 50 °C for 48 h; such hydrolytic conditions afforded **3b** in 73% yield.

It is remarkable that the ring opening of compounds **2a–f** occurs in a highly regioselective manner. Indeed, only trace amounts of side-products with the same molecular weights as compounds **3** were detected by gas chromatography–mass spectroscopy in the hydrolysis mixtures of compounds **2**. Elucidation of the regiochemistry of compounds **3a–f** was not easy and required non-conventional NMR experiments (see below). These results were confirmed by the X-ray crystal structure obtained for the triphenylmethyl derivative **3b**.

The preparation of tricyclic orthoamides by reaction of dimethylformamide dialkyl acetals with 1,4,7-triazacyclononane followed by hydrolysis to *N*-formyl derivatives has already been described.[17] Such reactions have also been used for the preparation of 1,4,7,10-tetraazacyclododecane-1-carbaldehyde, which is a key intermediate for the preparation of 1,4,7-trisubstituted TACD derivatives. In this case the *N*-formyl residue is used as a protective group for the fourth nitrogen atom and removed at the end by acidic hydrolysis.[13] It is noteworthy that the 2-(1,3-dioxolan-2-yl)ethyl group (*i.e.* in compounds **1c** and **3c**) can also be removed under the same hydrolytic conditions.[10] Therefore, derivative **3c** can be used conveniently for the preparation of 1,7-disubstituted TACD derivatives by further reaction (*e.g.* alkylation, acylation) at the two secondary nitrogen atoms followed by simultaneous cleavage of the formyl and 2-(1,3-dioxolan-2-yl)ethyl groups.

NMR characterization

TACD shows ^1H and ^{13}C NMR spectra with one signal only, in spite of the existence of conformers.[18] This is due to the interchange among conformers, which is too fast to be detected by NMR. Likewise, mono-*N*-alkylated derivatives show four signals for eight-ring carbons, again because of fast conformational interchange; even poly-*N*-alkylated TACD derivatives show fewer NMR signals than expected. Owing to this spectroscopic behaviour products **1a–f** give spectra that are sparse in information, in which signals can only be attributed in pairs on the basis of bidimensional correlation spectra [*i.e.* ^1H–^1H homonuclear chemical-shift correlation spectrum (COSY)[18–20] and ^1H–^{13}C heteronuclear chemical-shift correlation spectra (HETCOR)[21]]. The same is true for compounds **2a–f**, which, in spite of their conformational rigidity (due to the presence of two five membered fused rings), do not present as many different carbon signals at room temperature as might be expected.

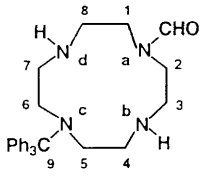


Fig. 1 Labelled structure of **3b**

However, when the substituent on the nitrogen atom is a formyl group, the conformational interchange is slowed sufficiently enough to allow all diastereotopic methylenes to become anisotropic, and thus eight signals to be picked up for the eight ring carbons. Although the spectra for **3a–f** appear complicated, the presence of the formyl group makes it possible to assign signals and to determine the positions of the substituents. The findings from a series of NMR experiments and from logical correlations enabled the regiochemistry of **3a–f** to be elucidated.

The strategy in ^1H and ^{13}C NMR signal assignment was firstly to assign conventional monodimensional ^1H and ^{13}C NMR spectra; secondly, to perform ^{13}C DEPT (distortionless enhancement by polarization transfer experiment) and ^{13}C INVGATE (inverse gated decoupled experiment) experiments to define the multiplicity of each carbon signal and the number of atoms responsible for each signal; and finally to carry out several bidimensional classical techniques, such as ^1H–^1H COSY, ^1H–^1H LRCOSY[22] (long-range homonuclear chemical shift correlation spectrum), ^1H–^{13}C HETCOR, INEPT (selective long-range insensitive nucleus enhancement by polarization transfer), COLOC[23] (correlated spectroscopy for long-range couplings), selective TOCSY[24] (totally correlated spectroscopy) and ^{13}C–^{13}C INADEQUATE[25] (incredible natural abundance double quantum transfer experiment), to define unambiguously the position of the substituents.

As an example, we report here the strategy adopted to define the structure of one compound of the series, namely 7-triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde (**3b**, see Fig. 1). ^1H and ^{13}C monodimensional NMR spectra are reported in Figs. 2–4.

^1H–^1H COSY (Fig. 5) and ^1H–^1H LRCOSY were used for determining 1-H, 2-H, 3-H and 8-H resonances; 1-H and 2-H were identified, by long-range coupling with the formyl

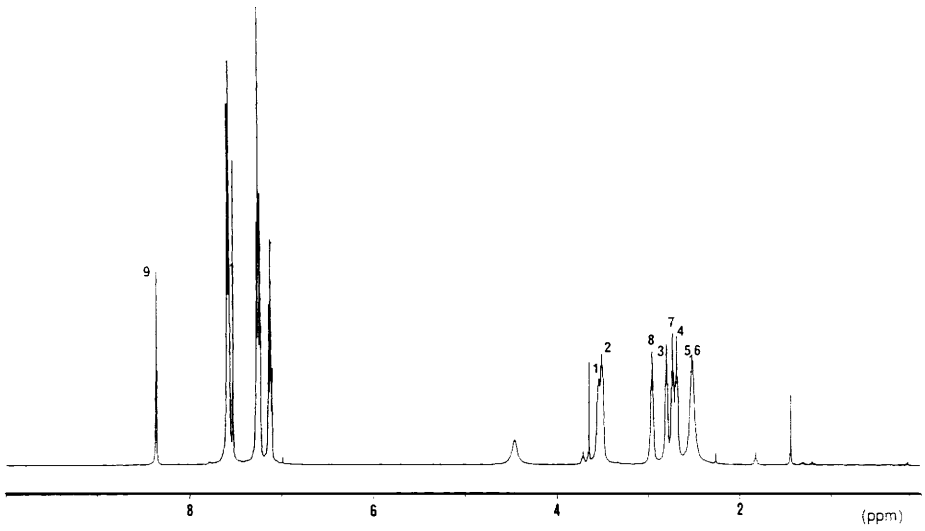


Fig. 2 ^{1}H monodimensional NMR spectrum of **3b**

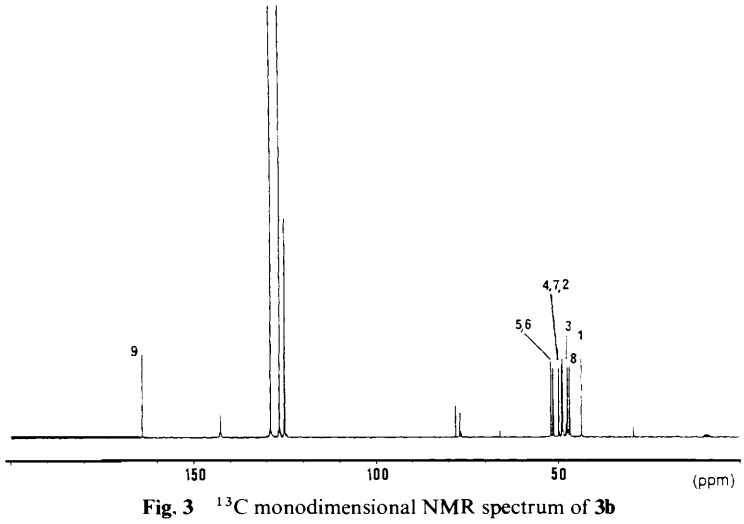


Fig. 3 ^{13}C monodimensional NMR spectrum of **3b**

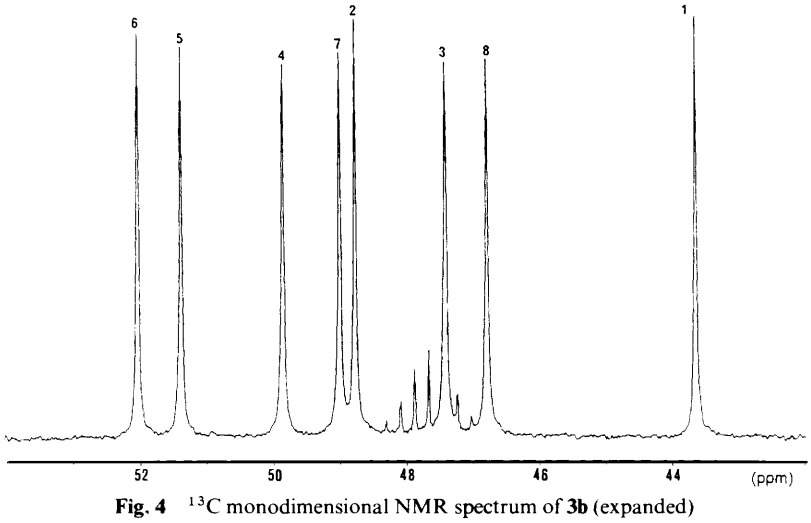


Fig. 4 ^{13}C monodimensional NMR spectrum of **3b** (expanded)

hydrogen, to be the more shifted signals (1-H 3.6 ppm, 2-H 3.5 ppm) which is to be expected because of the presence of an electron-withdrawing substituent on the nitrogen. On the basis of molecular models of TACD carbaldehyde, it is possible to see that one of the hydrogen atoms falls in the carbonyl shielding cone and the other in the deshielding cone: as a consequence, 1-H is shifted to lower fields than 2-H. The relationship between 1-H and 8-H and between 2-H and 3-H were defined both by the monodimensional homonuclear selective decoupling experiment and by ^{1}H–^{1}H LRCOSY.

A ^{1}H–^{13}C HETCOR (Fig. 6) experiment enabled C-1, C-2, C-3 and C-8 resonances to be assigned. C-1 is the signal at higher fields (43.7 ppm) confirming its *syn* position to the amide carbonyl oxygen and, indirectly, the position of 1-H in the carbonyl deshielding cone. C-2 is the signal at 48.8 ppm, confirming its *anti* position to the amide carbonyl oxygen and,

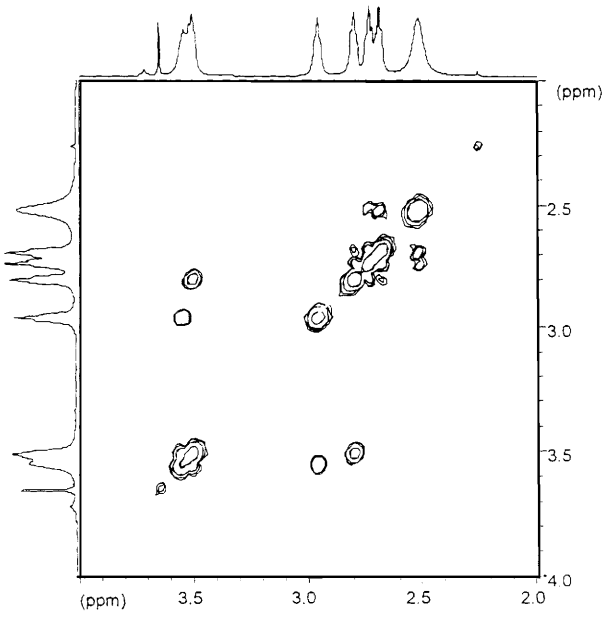


Fig. 5 COSY spectrum of **3b** (selected area)

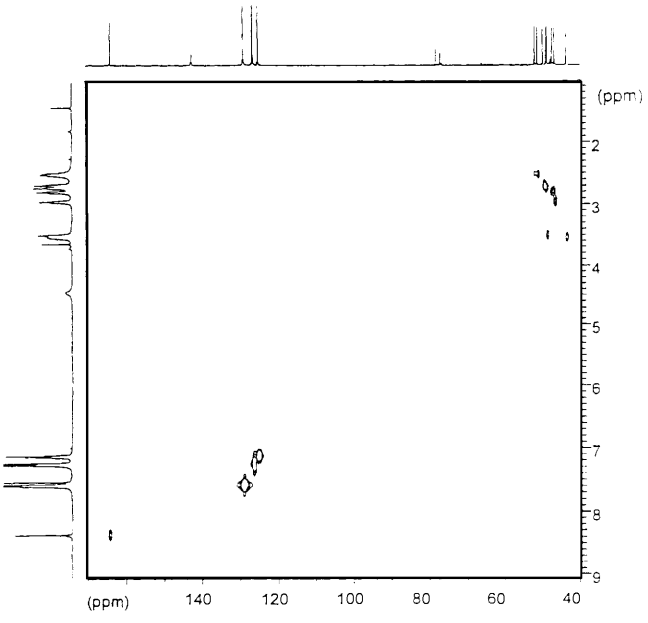


Fig. 6 HETCOR spectrum of **3b**

indirectly, the position of 2-H in the carbonyl shielding cone. C-3 and C-8 were identified directly on the basis of their connectivities with 3-H and 8-H, respectively.

The INADEQUATE (Fig. 7) experiment gave the ^{13}C–^{13}C connectivities: the signal at 52.1 ppm with the one at 49 ppm; the signal at 51.4 ppm with the one at 49.9 ppm; on this basis, the carbons at lower fields can be either C-5, C-6 or C-4, C-7 (not C-4, C-5 or C-6, C-7).

The COLOC experiment demonstrated long-range connectivities between the triphenylmethyl quaternary carbon and both hydrogen atoms on the carbons at lower fields (52.1 and 51.4 ppm). No long-range couplings occur between C-9 and C-3 or C-8. In particular C-9 is connected with the hydrogen atoms at higher fields [(2.5 ppm) with $^{LR}J_{CH}$ = 9.5 Hz], which are connected to carbons at lower fields (52.1 and 51.4 ppm) (^1H–^{13}C HETCOR experiment).

From these data, the triphenylmethyl group must be on N_c. Were it on N_b (or N_d), one of the couplings in the COLOC experiment would need to be a ^7J! Furthermore, the absence of

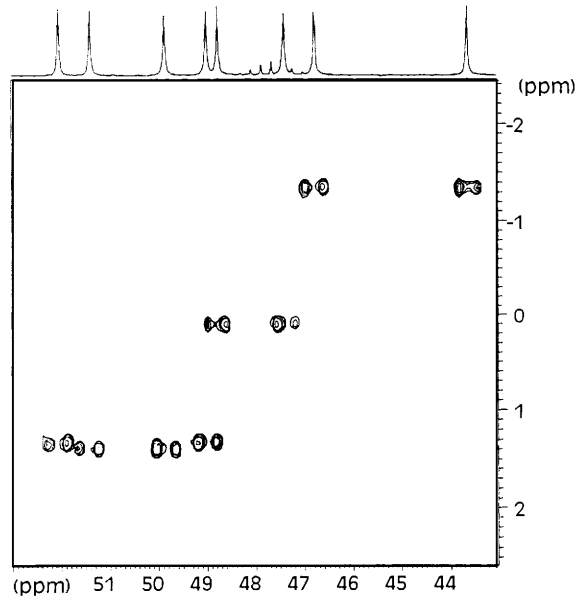


Fig. 7 INADEQUATE spectrum of **3b**

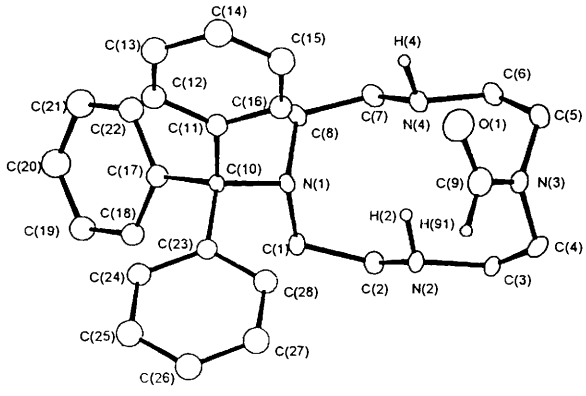


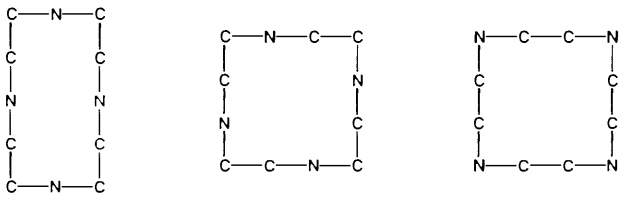
Fig. 8 ORTEP drawing showing the ligand **3b**

connectivity between C-9 and C-3 (or C-8) would be unreasonable.

Crystal structure of $C_{28}H_{34}N_4O{\cdot}0.5C_2H_6O$ (3b·0.5EtOH)

The crystal structure consists of the macrocyclic ligand $C_{28}H_{34}N_4O$ **3b** and of disordered ethanol molecules which are involved in short contacts (< 3 Å) with the atoms of the CHO group and with the N(2) atom. The macrocyclic ligand possesses a non-crystallographic pseudo-mirror plane passing through the N(1), N(3), C(9), C(10), C(17) and C(20) atoms, with only the oxygen and hydrogen atoms of the formyl moiety and the two hydrogens of the secondary nitrogen atoms not respecting the symmetry (see Fig. 8). On the other hand, the disorder showed by the CHO group in the crystal lattice is in accordance with this pseudo-symmetry. The two hydrogen atoms H(2) and H(4) have a 'head-to-tail' arrangement with the first one pointing inside the macrocyclic cavity. As expected, the nitrogen atom bearing the CHO group is contained in the plane of C(4), C(5) and C(9) carbon atoms (deviation from planarity is 0.025(6) Å). This feature confers higher rigidity to the macrocycle than shown by *N*-alkyl substituted TACD derivatives.

The conformation of the TACD ring can be described by the sequence of its dihedral angles as [2424],[26] with the methylene groups bound to the tertiary nitrogen atoms at the corners; as a consequence the macrocyclic ring has a rectangular shape (see Scheme 2). The atoms of the macrocyclic framework are



Scheme 2 Diagram representing: the [2424] conformation adopted by the ligand **3b** and the two possible [3333] conformations

disposed on three quasi parallel planes containing the first one N(1), N(3), H(2) and H(4), the second one C(1), N(2), C(4), C(5), N(4) and C(8), and the third one the remaining carbon atoms. This conformation allows the hydrogen atom H(2) to form a network of hydrogen bonds with all the other nitrogens [H(2)···N(4) 2.231(7), H(2)···N(3) 2.434(8) and H(2)···N(1) 2.450(7) Å]. To date structural studies on TACD and on derivatives obtained by substitution on carbon and nitrogen atoms, have revealed that the conformation for the uncomplexed ligand is always square [3333] with C atoms or N atoms occupying corner positions (see Scheme 2). To try to shed some light on the rather surprising [2424] conformation displayed by **3b** we have undertaken a conformational study using molecular mechanics calculations.

Molecular mechanics studies

We can hypothesize that the [2424] conformation found in **3b** is caused by either packing effects or by the type of substituent in the 1 and 7 positions. In fact, the conformation of the 12-membered ring could be influenced by either the triphenylmethyl group because of its rather high steric hindrance, or by the CO moiety which requires a planar geometry around the bound nitrogen atom. To verify these hypotheses we have chosen two structures[28,29] from the Cambridge Structural Database[30] that are representative of the two [3333] conformation types stated above. The energy content of conformers obtained by substituting the [3333] conformations in such structures with triphenylmethyl and formyl groups in the *trans* positions was calculated and compared with the energy content of **3b** obtained after geometry optimization of the X-ray structure. The two [3333] conformations have a significantly higher energy (see Table 1). This result allows us to exclude crystal packing forces as the reason for the shape of the macrocyclic ring.

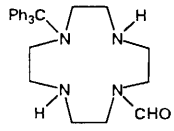
To verify the role played by the two substituents in determining the ring conformation we performed a geometry optimization of the macrocycles obtained after the replacement of either the triphenylmethyl moiety or the carbonyl group with a methyl residue. Again calculations were performed starting from conformation [2424] of **3b** and from those of the two structures having the [3333] conformation. Examination of the energy values of the three conformers obtained for each compound (7-methyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde **7** and 1-methyl-7-triphenylmethyl-1,4,7,10-tetraazacyclododecane **8**) shows that the replacement of the carbonyl group with the methyl group significantly destabilizes the [2424] macrocyclic conformation, while substitution of the triphenylmethyl group does not have an important effect on the energy trend.

These results indicate that the presence of the formyl moiety is the major factor contributing to the unusual conformation found for the TACD ring in **3b**. Therefore, we can infer that the stereochemical requirements determined by the sp^2 hybridization of the amide nitrogen atom dramatically influences the overall ring conformation.

Table 1 Energy contents of compounds 7-triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde **3b**, 7-methyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde **7** and 1-methyl-7-triphenylmethyl-1,4,7,10-tetraazacyclododecane **8** as obtained from molecular mechanics calculations

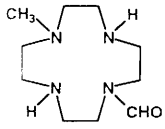
7-Triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde **3b**

Starting conformation	Energy contents (kcal mol^{-1})
[2424]	32.161
[3333] (N corners)	44.960
[3333] (C corners)	36.190



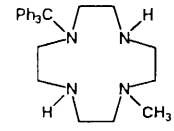
7-Methyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde **7**

Starting conformation	Energy contents (kcal mol^{-1})
[2424] I	−5.200
[3333] (N corners)	5.548
[3333] (C corners)	−6.444



1-Methyl-7-triphenylmethyl-1,4,7,10-tetraazacyclododecane **8**

Starting conformation	Energy contents (kcal mol^{-1})
[2424] I	44.660
[3333] (N corners)	37.856
[3333] (C corners)	27.693



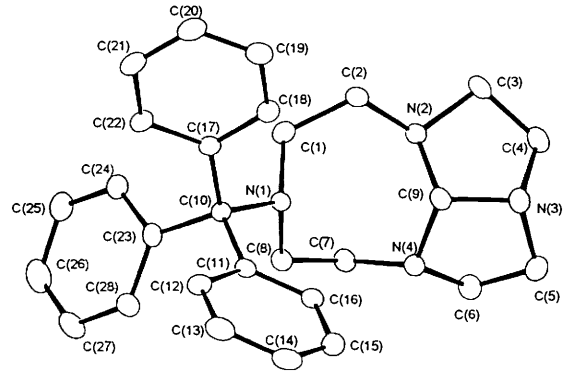
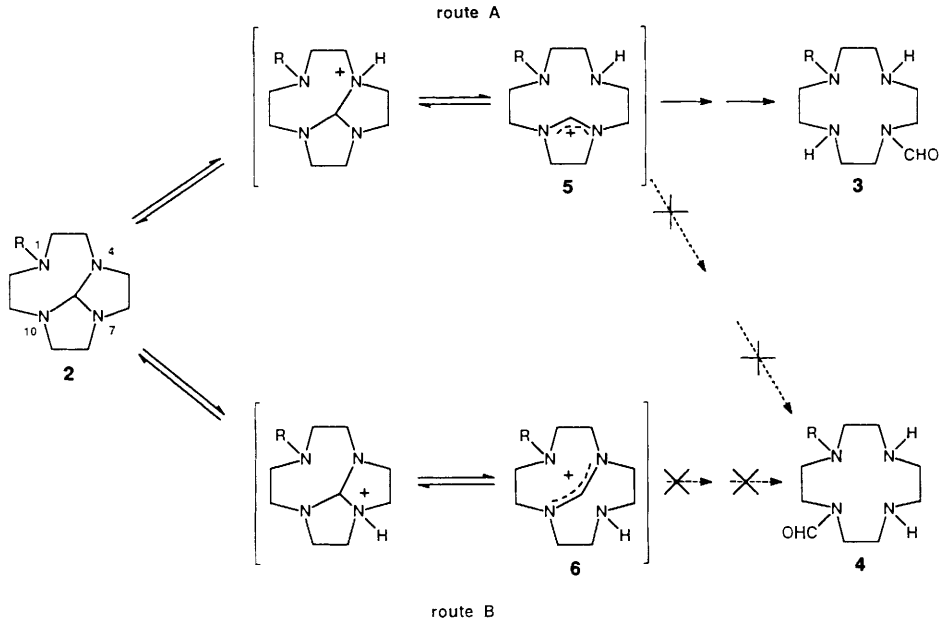


Fig. 9 ORTEP drawing showing the ligand **2b**

Crystal structure of $C_{28}H_{32}N_4 \cdot 1/6C_2H_6O$ (2b·1/6EtOH)

Our studies on the tricyclic intermediates **2** included several attempts to grow single crystals suitable for X-ray crystal structure analysis. Again we succeeded with the derivative bearing the bulky triphenylmethyl residue. To our knowledge this is the first solid-state structure of a polyazacycloalkane orthoamide so far reported. The crystal structure consists of the macrocyclic ligand $C_{28}H_{32}N_4$ **2b** and of disordered ethanol molecules lying around a $\bar{3}$ position. The 12-membered macrocycle is three-bridged by a carbon atom leading to a conformation (see Fig. 9) which differs from that found for the TACD ring of **3b**. In fact, even if the TACD ring of **2b** maintains the [2424] conformation, having four methylene carbons at the corners, the nitrogen disposition is of type II with the lone pair of the N(2) atom pointing toward the opposite side with respect to those of the other three nitrogen atoms. Also this TACD ring appears to possess a perpendicular non-crystallographic mirror plane, which in this case crosses the N(2) and N(4) atoms. The macrocycle does not seem to have intra-annular H···H interactions, whereas it is interesting to observe that the N(1) atom is involved in a weak contact with the hydrogen of the bridging C(9) carbon atom [N(1)···H(9)



Scheme 3

2.775(6) Å]. Calculations performed on the mean planes of the three rings generated by the bridging C(9) atom have shown that the 8-membered ring forms dihedral angles of 33.1(2) and 26.6(1)° with the two 5-membered rings, which themselves are at an angle of 57.6(2)° with each other.

Conclusions

Reaction of monoalkylated TACD **1** with dimethylformamide diethyl acetal followed by hydrolysis of the resulting triprotected species **2** offers a very selective and high yielding access to 7-substituted derivatives of 1,4,7,10-tetraazacyclododecane-1-carbaldehyde. In particular, the unexpected regioselectivity observed for the hydrolytic ring opening of tricyclic orthoamides **2** deserves some comment. The mechanism possibly involved in the hydrolysis is shown in Scheme 3 and, accordingly, the reaction should afford a mixture of **4** and **3**. However, formation (if any) of the 1,4-isomer **4** is negligible, a situation that suggests the hydrolysis does not occur by route B. The formation of the bicyclic intermediate **6** is possibly prevented by the strain associated with the CH group joining N(4) and N(10). Even more surprising is the opening of the five-membered ring in intermediate **5**, which leads to the formation of **3** only; according to route A two pathways could be followed. A tentative explanation of this result is that, after addition of a water molecule to the carbocation of intermediate **5**, the protonation of N(10), which should be the driving force behind the formation of 1,7-substituted derivatives, is more favourably assisted by the tertiary N(1) atom than is the protonation of N(7) by the secondary N(4) atom.

Derivatives **3** can be used as intermediates for the regiocontrolled preparation of TACD derived ligands bearing different side arms on the nitrogen atoms. In this respect the choice of suitable monoalkylated TACD derivatives opens the way to the synthesis of a variety of polysubstituted ligands. Furthermore, the recent development of selective and high yielding methodologies for the monoalkylation of TACD,[4,15] without using a large excess of the macrocycle, makes the preparation of derivatives **3** easier and, possibly, less expensive.

Experimental

General

Routine ^1H and ^{13}C NMR spectra for compound characterization were recorded on a Bruker AC200 spectrometer, equipped with a 5 mm dual probe, using deuterium as lock signal. Mass spectra were recorded on a VG 7070EQ spectrometer, using the FAB ionization technique with glycerol as the matrix. Mps were determined on a Buchi 510 apparatus and are uncorrected. TLC analyses were performed using E. Merck precoated silica 60F254 plates. Purification by column chromatography were carried out on E. Merck silica gel 60 (230–400 mesh).

General procedure for the preparation of monoalkylated TACD 1a–f

To a solution of TACD[6] (50 g, 0.29 mol) in acetonitrile (500 cm^3) at reflux under a nitrogen atmosphere was added in 2 h a solution of the appropriate alkyl bromide (0.029 mol) in acetonitrile (250 cm^3). After 1 h the solution was cooled to 5 °C and left at this temperature for 15 h; a mixture of TACD and TACD hydrobromide precipitated out. The mixture was filtered and the filtrate was evaporated under reduced pressure. Work-up thereafter was different for **1b–e** (work-up a) and **1a,f** (work-up b).

Work-up a. The residue was dissolved in 5% aqueous $NaHCO_3$ (200 cm^3) and extracted with toluene (3 × 200 cm^3). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was crystallized from light petroleum (bp 40–60 °C).

Work-up b. By crystallization of the residue from ethyl acetate a further portion of TACD was recovered. After filtration the solution was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with propan-2-ol–chloroform–triethylamine (6:4:2) as the eluent.

1-Benzyl-1,4,7,10-tetraazacyclododecane 1a. Work-up a yielded the title compound as a white solid (89%); mp 85 °C; δ_H(200 MHz; $CDCl_3$) 2.4 (8 H, m), 2.5 (4 H, m), 2.6 (4 H, br t), 3.4 (2 H, br s) and 7.2 (5 H, m); δ_C(50 MHz; $CDCl_3$) 44.90,

46.13, 46.98, 51.03, 59.04, 126.84, 128.11, 128.80 and 138.74; *m/z* 263 ($M + H^+$) (Found: C, 68.5; H, 10.0; N, 21.15. $C_{15}H_{26}N_4$ requires C, 68.7; H, 10.0; N, 21.35%).

1-Triphenylmethyl-1,4,7,10-tetraazacyclododecane 1b. Work-up b yielded the title compound as a white solid (75%); mp 70–71 °C; δ_H(200 MHz; $CDCl_3$) 2.9–3.5 (16 H, m) and 7.5–8.3 (15 H, m); δ_C(50 MHz; $CDCl_3$) 43.60, 47.29, 49.47, 54.42, 79.37, 126.13, 127.55, 129.95 and 143.72; *m/z* 415 ($M + H^+$) (Found: C, 78.0; H, 8.3; N, 13.4. $C_{27}H_{34}N_4$ requires C, 78.2; H, 8.3; N, 13.5%).

1-[2-(1,3-Dioxolan-2-yl)ethyl]-1,4,7,10-tetraazacyclododecane 1c. Work-up b yielded the title compound as a colourless oil (86%); δ_H(200 MHz; $CDCl_3$) 1.9 (2 H, m), 2.6–2.7 (14 H, m), 2.85 (4 H, m), 3.8–4.0 (4 H, m) and 4.9 (1 H, t); δ_C(50 MHz; $CDCl_3$) 31.05, 44.58, 45.69, 46.53, 48.76, 50.96, 64.29 and 102.93; *m/z* 273 ($M + H^+$) (Found: C, 56.9; H, 10.5; N, 20.8. $C_{13}H_{28}N_4O_2$ requires C, 57.3; H, 10.4; N, 20.6%).

1-(1,3-Dioxolan-2-ylmethyl)-1,4,7,10-tetraazacyclododecane 1d. Work-up b yielded the title compound as a colourless oil (88%); δ_H(200 MHz; $CDCl_3$) 2.7–3.0 (18 H, m), 4.0–4.2 (4 H, m) and 5.1 (1 H, t); δ_C(50 MHz; $CDCl_3$) 44.81, 45.94, 46.62, 51.92, 56.68, 64.45 and 103.06; *m/z* 259 ($M + H^+$) (Found: C, 56.1; H, 10.3; N, 21.9. $C_{12}H_{26}N_4O_2$ requires C, 55.8; H, 10.1; N, 21.7%).

1-(2,2-Dimethoxyethyl)-1,4,7,10-tetraazacyclododecane 1e. Work-up b yielded the title compound as a colourless oil (95%); δ_H(200 MHz; D_2O) 2.4–2.7 (18 H, m), 3.4 (6 H, br s) and 4.45 (1 H, t); δ_C(50 MHz; D_2O) 46.16, 47.48, 47.90, 54.28, 57.21, 58.26 and 106.81; *m/z* 261 ($M + H^+$) (Found: C, 55.1; H, 10.7; N, 21.3. $C_{12}H_{28}N_4O_2$ requires C, 55.35; H, 10.8; N, 21.5%).

***tert*-Butyl 1,4,7,10-tetraazacyclododecan-1-ylacetate 1f**. Work-up a yielded the title compound as a colourless oil (58%); δ_H(200 MHz; $CDCl_3$) 1.75 (9 H, br s), 2.85–3.15 (16 H, m) and 3.6 (2 H, br s); δ_C(50 MHz; $CDCl_3$) 27.29, 44.49, 45.80, 46.71, 51.54, 56.78, 80.65 and 170.08; *m/z* 287 ($M + H^+$) (Found: C, 58.6; H, 10.6; N, 19.5. $C_{14}H_{30}N_4O_2$ requires C, 58.7; H, 10.6; N, 19.6%).

General procedure for the preparation of the tricyclic derivatives 2a–f

A solution of monoalkylated TACD (15 mmol) and dimethylformamide diethyl acetal (2.42 g, 16.5 mmol) in benzene (40 cm^3) was heated at 80 °C. The benzene–ethanol azeotrope was distilled from a Claisen condenser until the conversion was complete by GLC analysis. The solution was evaporated under reduced pressure to give the product.

7-Benzyloctahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta-[*cd*]pentalene 2a. The title compound was obtained as a pale yellow oil (98%); δ_H(200 MHz; $CDCl_3$) 2.3–3.0 (16 H, m), 3.6 (2 H, s), 5.0 (1 H, s) and 7.1–7.3 (5 H, m); δ_C(50 MHz; $CDCl_3$) 50.93, 51.86, 52.42, 55.25, 63.28, 97.73, 126.76, 127.97, 129.09 and 139.62; *m/z* 273 ($M + H^+$) (Found: C, 70.5; H, 8.9; N, 20.5. $C_{16}H_{24}N_4$ requires C, 70.55; H, 8.9; N, 20.6%).

7-Triphenylmethyloctahydro-5*H*,9b*H*-2a,4a,7,9a-tetraaza-cycloocta[*cd*]pentalene 2b. The title compound was obtained as a white solid (98%); mp 180–183 °C; δ_H(200 MHz; $CDCl_3$) 2.2–2.4 (2 H, m), 3.1–3.7 (14 H, m), 5.85 (1 H, s) and 7.5–8.1 (15 H, m); δ_C(50 MHz; $CDCl_3$) 51.50, 52.53, 53.29, 79.71, 98.58, 128.11, 127.56, 130.05 and 143.90; *m/z* 425 ($M + H^+$) (Found: C, 79.5; H, 7.6; N, 12.9. $C_{28}H_{32}N_4$ requires C, 79.2; H, 7.6; N, 13.2%). Slow evaporation of an ethanolic solution of the compound gave a single crystal suitable for X-ray analysis.

7-[2-(1,3-Dioxolan-2-yl)ethyl]octahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene 2c. The title compound was obtained as a colourless oil (98%); δ_H(200 MHz; $CDCl_3$) 2.0–2.2 (2 H, m), 2.7–3.5 (18 H, m), 4.1–4.4 (4 H, m), 5.17 (1 H, s) and 5.22 (1 H, t); δ_C(50 MHz; $CDCl_3$) 31.05, 49.84, 50.90, 51.98, 52.45, 55.23, 64.43, 98.48 and 102.89; *m/z* 283 ($M + H^+$) (Found: C, 59.7; H, 9.3; N, 19.5. $C_{14}H_{26}N_4O_2$ requires C, 59.5; H, 9.3; N, 19.8%).

7-(1,3-Dioxolan-2-ylmethyl)octahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta[*cd*]pentalene 2d. The title compound was obtained as a colourless oil (97%); δ_H(200 MHz; $CDCl_3$) 2.1–3.0 (18 H, m), 3.5–3.8 (4 H, m), 4.67 (1 H, s) and 4.73 (1 H, t); δ_C(50 MHz; $CDCl_3$) 50.80, 52.07, 52.71, 56.01, 60.61, 64.44, 98.37 and 103.94; *m/z* 269 ($M + H^+$) (Found: C, 57.9; H, 9.2; N, 20.6. $C_{13}H_{24}N_4O_2$ requires C, 58.2; H, 9.0; N, 20.9%).

7-(2,2-Dimethoxyethyl)octahydro-5*H*,9b*H*-2a,4a,7,9a-tetra-azacycloocta[*cd*]pentalene 2e. The title compound was obtained as a colourless oil (98%); δ_H(200 MHz; $CDCl_3$) 2.1–2.9 (18 H, m), 3.1 (6 H, s), 4.2 (1 H, t) and 4.6 (1 H, s); δ_C(50 MHz; $CDCl_3$) 50.99, 52.19, 52.79, 53.43, 56.16, 59.75, 99.28 and 103.84; *m/z* 271 ($M + H^+$) (Found: C, 57.4; H, 9.8; N, 20.5. $C_{13}H_{26}N_4O_2$ requires C, 57.7; H, 9.7; N, 20.7%).

***tert*-Butyl octahydro-5*H*,9b*H*-2a,4a,7,9a-tetraazacycloocta-[*cd*]pentalen-7-ylacetate 2f**. The title compound was obtained as a colourless oil (97%); δ_H(200 MHz; $CDCl_3$) 1.75 (9 H, s), 2.8–3.35 (16 H, m), 3.65 (2 H, s) and 5.2 (1 H, s); δ_C(50 MHz; $CDCl_3$) 27.79, 50.51, 51.77, 52.36, 54.64, 59.13, 80.16, 99.58 and 170.66; *m/z* 297 ($M + H^+$) (Found: C, 60.65; H, 9.4; N, 18.7. $C_{15}H_{28}N_4O_2$ requires C, 60.8; H, 9.5; N, 18.9%).

General procedure for the preparation of the carbaldehyde derivatives 3a,c,d,e

A solution of the tricyclic derivative (15 mmol) in ethanol–water (1:1; 50 cm^3) was stirred at room temperature for 2 h. The solution was evaporated at reduced pressure to give a residue that was purified as described below.

7-Benzyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde 3a. After crystallization from ethyl acetate the title compound was obtained as a white solid (80%); mp 64–65 °C; δ_H(200 MHz; $CDCl_3$) 2.6 (8 H, m), 2.7 (2 H, t), 2.9 (2 H, t), 3.4 (2 H, t), 3.5 (2 H, t), 3.6 (2 H, s), 7.2–7.3 (5 H, m) and 8.1 (1 H, s); δ_C(50 MHz; $CDCl_3$) 44.40, 46.70, 46.80, 47.05, 47.30, 49.94, 50.15, 51.15, 59.39, 126.72, 128.03, 128.51, 139.31 and 164.20; *m/z* 291 ($M + H^+$) (Found: C, 66.2; H, 9.1; N, 19.3. $C_{16}H_{26}N_4O$ requires C, 66.15; H, 9.0; N, 19.3%).

7-[2-(1,3-Dioxolan-2-yl)ethyl]-1,4,7,10-tetraazacyclo-dodecane-1-carbaldehyde 3c. After crystallization from ethyl acetate the title compound was obtained as a waxy solid (83%); δ_H(200 MHz; $CDCl_3$) 2.1 (2 H, t), 2.7–3.1 (14 H, m), 3.75 (4 H, m), 4.2 (4 H, br d) 5.2 (1 H, t), and 8.1 (1 H, s); δ_C(50 MHz; $CDCl_3$) 31.13, 44.37, 46.70, 46.84, 46.97, 47.10, 49.55, 49.99, 50.45, 51.02, 64.53, 102.82 and 164.23; *m/z* 301 ($M + H^+$) (Found: C, 55.8; H, 9.4; N, 18.5. $C_{14}H_{28}N_4O_3$ requires C, 56.0; H, 9.4; N, 18.65%).

7-(1,3-Dioxolan-2-ylmethyl)-1,4,7,10-tetraazacyclododecane-1-carbaldehyde 3d. The residue was purified by column chromatography on silica gel with chloroform–6 mol dm^{-3} ammonia in methanol (8.5:1.5) as the eluent to give the title compound as a colourless oil (80%); δ_H(200 MHz; $CDCl_3$) 2.0–2.5 (16 H, m), 3.0–3.2 (4 H, m), 3.4–3.6 (4 H, m), 4.45 (1 H, t) and 7.8 (1 H, s); δ_C(50 MHz; $CDCl_3$) 44.37, 46.72, 46.85, 46.93, 47.03, 49.92, 51.65, 51.94, 56.74, 64.65, 102.85 and 164.31; *m/z* 287 ($M + H^+$) (Found: C, 54.25; H, 9.2; N, 19.3. $C_{13}H_{26}N_4O_3$ requires C, 54.5; H, 9.2; N, 19.6%).

7-(2,2-Dimethoxyethyl)-1,4,7,10-tetraazacyclododecane-1-carbaldehyde 3e. The residue was purified by column chromatography on silica gel with chloroform–6 mol dm^{-3} ammonia in methanol (8.5:1.5) as the eluent to give the title compound as a colourless oil (86%); δ_H(200 MHz; $CDCl_3$) 2.0–2.5 (16 H, m), 3.0 (6 H, s), 3.1–3.3 (4 H, m), 4.0 (1 H, t) and 7.8 (1 H, s); δ_C(50 MHz; $CDCl_3$) 44.12, 46.58, 46.77, 46.88, 49.71, 51.45, 51.88, 53.66, 56.67, 103.09 and 164.12; *m/z* 289 ($M + H^+$) (Found: C, 54.4; H, 9.9; N, 19.2. $C_{13}H_{28}N_4O_3$ requires C, 54.1; H, 9.8; N, 19.4%).

7-Triphenylmethyl-1,4,7,10-tetraazacyclododecane-1-carbaldehyde 3b. *Procedure in* EtOH–*water*.—Compound **2b** was dissolved in boiling ethanol (100 cm^3) and the solution after dilution with water (50 cm^3) was heated at reflux for 4 h. It was then evaporated under reduced pressure and the residue purified by column chromatography on silica gel with ethyl acetate–6 mol dm^{-3} ammonia in methanol (3:1) as the eluent. After crystallization from ethyl acetate the title compound was obtained as a white solid (33%); mp 160–163 °C; δ_H(200 MHz: $CDCl_3$) 2.2–3.1 (14 H, m), 3.35–3.65 (4 H, m), 7.0–7.6 (15 H, m) and 8.4 (1 H, s); δ_C(50 MHz; $CDCl_3$) 44.33, 48.19, 49.05, 49.91, 50.46, 50.78, 52.72, 52.78, 79.07, 125.84, 127.34, 129.82, 143.54 and 164.30; *m/z* 443 ($M + H^+$) (Found: C, 75.8; H, 7.8; N, 12.4. $C_{28}H_{34}N_4O$ requires C, 76.0; H, 7.7; N, 12.65%). A single crystal of the compound suitable for X-ray analysis was obtained by slowly cooling (from 76 °C to room temperature) a 5% (w/w) solution of **3b** in ethyl acetate.

Procedure in THF–*water*.—Compound **2b** (3.4 mmol) was dissolved in THF (60 cm^3) and the solution after dilution with water (30 cm^3) was heated to 50 °C and left for 48 h. Removal of the THF by evaporation precipitated a white solid which was filtered off and purified by column chromatography on silica gel with chloroform–methanol–25% aqueous ammonia (8:2:0.2) as eluent. The product was identical with the one obtained by the previous procedure.

***tert*-Butyl 7-formyl-1,4,7,10-tetraazacyclododecan-1-ylacetate 3f**. Compound **2f** (15 mmol) was dissolved in ethanol–water (1:1; 800 cm^3) and the solution stirred for 18 h. After this it was evaporated under reduced pressure and the residue purified by column chromatography on silica gel with methanol–25% aqueous ammonia (10:1) as the eluent to give the title compound as a colourless oil (67%); δ_H(200 MHz: $CDCl_3$) 1.4 (9 H, s), 2.4–2.7 (12 H, m), 3.2 (2 H, s), 3.3–3.5 (4 H, m) and 8.0 (1 H, s); δ_C(50 MHz; $CDCl_3$) 27.71, 44.23, 46.37, 46.70, 46.93, 49.57, 50.51, 51.70, 55.77, 80.38, 164.37 and 170.68; *m/z* 315 ($M + H^+$) (Found: C, 57.5; H, 9.75; N, 17.9. $C_{15}H_{30}N_4O_3$ requires C, 57.3; H, 9.6; N, 17.8%).

NMR experiments

All experiments were recorded with 0.1 mol dm^{-3} solutions in $CDCl_3$ in a 5 mm tube on a Bruker AMX400 Fourier Transformer spectrometer operating at 400.13 and 100.61 MHz for ^1H and ^{13}C, respectively. All chemical shifts were determined relative to TMS. For INADEQUATE experiments 1 mol dm^{-3} solutions were used. Data acquisition and processing were performed under similar conditions according to Bruker standard pulsed programs. In particular, the ^1H $\pi_{90°}$ transmitter pulse was 14.5 μs, the ^1H $\pi_{90°}$ decoupler pulse 13 μs, and the ^{13}C $\pi_{90°}$ transmitter pulse 6.1 μs.

Crystal data

$C_{28}H_{34}N_4O{\cdot}0.5C_2H_6O$, $M = 465.6$. Monoclinic, $a = 11.593(3)$, $b = 13.117(10)$, $c = 15.934(5)$ Å, $\beta = 90.81(2)°$, $V = 2423(2)$ $Å^3$ (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, $\lambda = 1.5418$ Å), space group $P2_1/n$ (alt. $P2_1/c$, No.14), $Z = 4$. $D_x = 1.29$ g cm^{-3}. Prismatic, colourless crystal, approximate dimensions 0.6 × 0.4 × 0.3 mm, μ(Cu-Kα) = 5.51 cm^{-1}.

$C_{28}H_{32}N_4{\cdot}1/6C_2H_6O$, $M = 432.25$. Rhombohedral, $a = b = 31.95(1)$, $c = 11.80(1)$ Å (hexagonal cell), $V = 10\,434(10)$ $Å^3$ (by least-squares refinement of 25 automatically centred reflections, $\lambda = 0.710\,69$ Å), space group $R\bar{3}$ (No.148), $Z = 18$, $D_x = 1.24$ g cm^{-3}. Prismatic, colourless crystal, approximate dimensions 0.7 × 0.3 × 0.2 mm, μ(Mo-Kα) = 0.74 cm^{-1}.

Data collection and processing. Both data reflections were collected by using an Enraf-Nonius CAD4 X-ray diffractometer.

$C_{28}H_{34}N_4O{\cdot}1/2C_2H_6O$, θ–2θ scan mode with a variable scan width of (1.0 + 0.14 tg θ)° scan rate of 4 deg min^{-1}, graphite-monochromatized Cu-Kα radiation; 3654 independent reflections collected ($5 \leqslant 2\theta \leqslant 114°$, h, $+k$, $+l$), giving 1693 reflections with $I > 3\sigma(I)$. Lorentz and polarization effects corrections applied; an absorption correction was practised once the structure was solved by using the Walker and Stuart method.[31] Three standard reflections were monitored during data collection: no loss of intensity was detected.

$C_{28}H_{32}N_4{\cdot}1/6C_2H_6O$, θ–2θ scan mode with a variable scan width of (0.7 + 0.35 tg θ)° variable scan rate, graphite-monochromatized Mo-Kα radiation; 3032 independent reflections collected ($5 \leqslant 2\theta \leqslant 45°$, $+h$, $+k$, l), giving 1661 reflections with $I > 2\sigma(I)$. Lorentz and polarization effects corrections applied. Three standard reflections were monitored during data collection: no loss of intensity was detected.

Structure analysis and refinement. $C_{28}H_{34}N_4O{\cdot}1/2C_2H_6O$, direct methods of SIR88.[32] Full-matrix least-squares technique. The function minimized was $\Sigma w(F_o - F_c)^2$ with $w = a/\sigma^2(F)$ where a is an adjustable parameter. The carbon atoms of the three phenyl rings were refined as rigid groups with D_{6h} idealized geometry, with individual isotropic temperature factors. The other non-hydrogen atoms of the macrocycle were treated anisotropically. A ΔF Fourier synthesis clearly showed the positions of the hydrogen atoms of the two secondary nitrogen atoms of the macrocycle and two maxima localized around a symmetry centre due to the presence of a molecule of ethanol. These disordered atoms, therefore, were refined as isotropic carbon atoms with multiplicity factors of 0.5. The ΔF Fourier map showed that also the oxygen atom of the formyl group is in a disordered array, mutually changing its position with that of the hydrogen atom of the CHO group. The population parameters of these positions converged in the refinement to values of 0.84 and 0.16, respectively. The hydrogen atoms of the ligand molecules were all introduced in calculated positions and their coordinates refined in agreement with those of the linked atoms with an overall isotropic temperature factor U of 0.06 $Å^2$. The final agreement factors were $R = 0.085$ and $R_w = 0.091$. All calculations were performed with the SHELX-76 set of programs.[33]

$C_{28}H_{32}N_4{\cdot}1/6C_2H_6O$, direct methods of MULTAN-78.[34] Full matrix least-squares refinement by using SHELXL-93,[35] with weighting scheme parameters of 0.0815 and 0.00. The hydrogen atoms of the tetraaza macrocycle were introduced in calculated positions and refined accordingly to the linked atoms with an overall temperature factor refined to 0.056 $Å^2$. Anisotropic thermal parameters were used for all the non-hydrogen atoms of the molecule. A difference Fourier map showed the presence of two electronic density peaks which were attributed to a disordered solvent molecule of ethanol, one of these being localized on the $\bar{3}$ symmetry centre and refined with an isotropic temperature factor. The final R factor was 0.0525, whereas the $wR2$ factor was 0.167 with $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{\frac{1}{2}}$. Both refinement programs use the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all the atoms from the International Tables for Crystallography.[36] The molecular plots were produced by the ORTEP[37] program. Tables of thermal parameters, fractional atomic coordinates and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.‡

Computational details section

All the molecular modelling studies were accomplished by using the software programs provided by Biosym Technologies:[38]

‡ For details of the system, see *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

InsightII and Discover version 2.2.0. The force field used to optimize the molecular geometry was CFF91; the minimization algorithms were steepest descent first, then conjugate gradient and finally Newton-Raphson. The convergence criterion utilized to stop the minimization procedure was rms derivative = 0.001 kcal mol^{-1} $Å^{-1}$. All calculations were performed on an IBM RISC/6000 computer, model 320 H.

Acknowledgements

We thank Dr Miles Kirchin for critical linguistic revision of the manuscript.

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Paper 5 03463I
Received 31*st May* 1995
Accepted 14*th July* 1995