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3-[2,6-Bis(diethylcarbamoyl)pyridin-4-yl]-N-(tert-butoxycarbonyl)alanine methyl ester: a chiral tridentate ligand that causes a diastereomeric excess of its lanthanide complexes in solution

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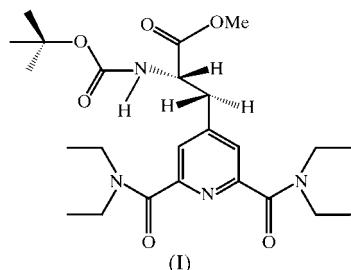
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L^4 , or 3-[2,6-bis(diethylcarbamoyl)pyridin-4-yl]-N-(tert-butoxycarbonyl)alanine methyl ester, $C_{24}H_{38}N_4O_6$, crystallizes in neat [010] laths stabilized by abundant intra- and intermolecular hydrogen bonds. The strongest of these form [010] chains of molecules, thus rationalizing the fastest growth direction, while the slowest direction coincides with the normal to the (110) layers, which are linked by very weak hydrogen bonds. There exist two independent molecules, the distances and bond angles of which differ in a random manner only. The torsion and dihedral angles, however, differ so as to achieve optimal packing. The influence of the chiral group in the 4-position of the pyridine ring on the helical wrapping and on the ensuing diastereomeric induction is briefly discussed.

Comment

Lanthanide coordination chemistry is essentially motivated by applications in biology and medicine, mainly for analysis



(Parker, 2000) and diagnosis (Yam & Lo, 1999), but also for therapeutics (Guo & Sadler, 1999). These applications require

precise control of the Ln^{III} inner coordination sphere and therefore ligands that preserve, or preferably enhance, the physicochemical properties of the metal ion.

We have recently turned our attention to mononuclear triple helical lanthanide complexes with chiral tridentate aromatic ligands for the purpose of studying the influence of helical wrapping on diastereomeric induction, thermodynamic properties and energy-transfer processes. Related helical induction in the ground state requires diastereomeric resolution, and we have recently synthesized the title compound, L^4 , (I), bearing a chiral group in the 4-position of the pyridine ring. We have also studied the interaction of L^4 with trivalent lanthanide ions (Muller, Schmidt *et al.*, 2001). Interest in synthesizing chiral helices is growing, because they may be incorporated in, for example, biomedical materials and used as

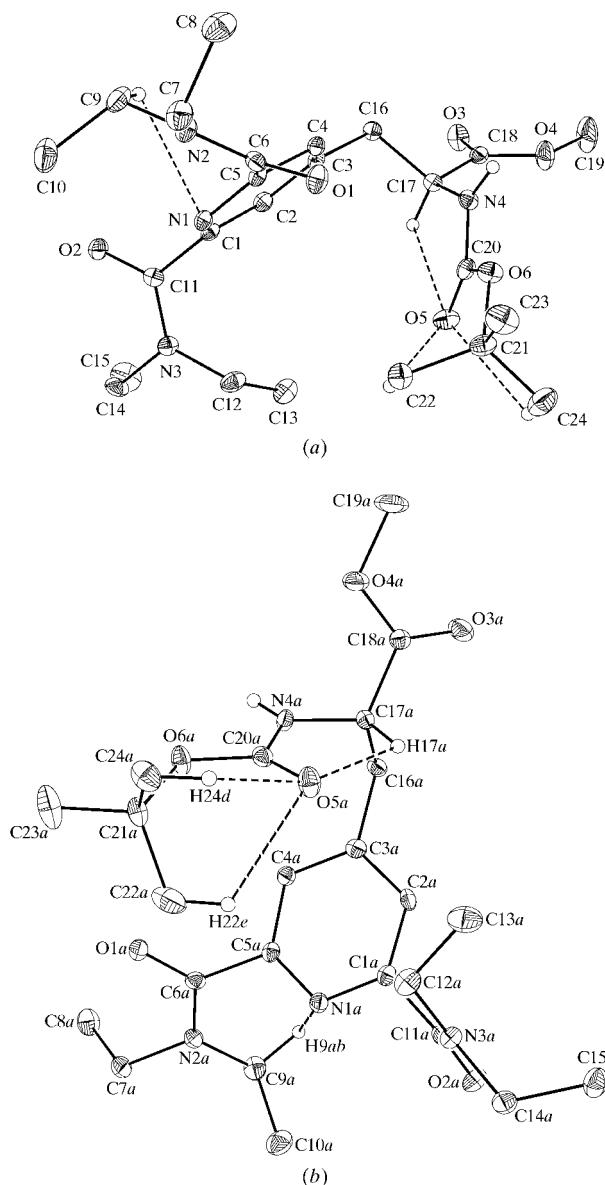


Figure 1

The atom-numbering scheme and intramolecular hydrogen bonding (dashed lines) for the two independent molecules of L^4 . Displacement ellipsoids are shown at the 40% probability level.

probes for chirality sensing of biological substances (Tsukube & Shinoda, 2002; Govenlock *et al.*, 1999).

NMR analysis of L⁴ is consistent with the presence of a single species, with a terdentate binding unit in a *trans-trans* conformation. The absolute configuration of the asymmetric C atom is retained, as demonstrated by the value of the specific optical rotation, *viz.* $[\alpha]_{D}^{25} = -3.5(4)^\circ \text{ dm}^2 \text{ mol}^{-1}$ (Muller, Schmidt *et al.*, 2001). We have determined the crystal structure of L⁴ in order to confirm that the *trans-trans* conformation observed in solution also prevails in the solid state.

The structure contains two independent molecules, which are depicted in Fig. 1. These are roughly equivalent by a translation of $\frac{1}{2}c$. A normal probability plot (NPP; Abrahams & Keve, 1971) involving 34 distances and 45 bond angles that are analogous in the two molecules is linear, with a slope of 1.60 and a δm_{exp} axis intercept of -0.05. The linearity implies that these geometric quantities differ only in a random way between the two molecules, while the non-unit slope points to an underestimation of the variances. The molecules do, however, distinguish themselves in their torsion and dihedral angles. In each molecule there are seven subsets of atoms that define planes, *viz.* the pyridine ring, the C5/C6/C7/C9/N2/O1 and C1/C11/C12/C14/N3/O2 carboxamide groups, the C3/C16/C17/C18 butane skeleton, the C17/C18/C19/N4/O3/O4 aminoacetic acid methyl ester group, the C20/C21/O5/O6 aminocarboxylate group, and the C17/C20/N4 azapropane group. Of the seven planes, the atoms in the C3a/C16a/C17a/C18a group exhibit the largest mean deviation from the plane (0.06 Å). The angles between the planes of the aminocarboxylate and azapropane groups are 16.8 (2) and 12.1 (4)° for the two molecules. The values of these angles must be due

to steric requirements, notwithstanding the intramolecular O··H—C hydrogen bonds (Table 1) that favor the planar configuration, since the distances and angles between analogous atoms in the aminocarboxylate and carboxamide groups are very similar in the two molecules, and since these groups are perfectly planar. Furthermore, the C=O and C≡N distances (Table 2) indicate some degree of delocalization in the amide groups.

The structure is stabilized by a wealth of intermolecular hydrogen bonds, which form a three-dimensional network (Fig. 2 and Table 1). The strongest of these ($\text{O}\cdots\text{H}-\text{N}$) form [010] chains of molecules, each consecutive pair of molecules being related by $\{C_{2y}|0\ \frac{1}{2}\ 0\}$. These chains, in turn, are linked by weak $\text{O}\cdots\text{H}-\text{C}$ hydrogen bonds to form *ab* layers that are finally connected by even weaker $\text{O}\cdots\text{H}-\text{C}$ bonds to complete the three-dimensional web. The strength of the hydrogen bonds agrees with the observed growth speeds of the crystal faces, *viz.* $v_{010} >> v_{101} > v_{100}$ (L^4 grows as [010] joists). None of the hydrogen bonds (Table 1) rigorously qualify according to the Desiraju (1996) criteria ($2.0 < d < 2.3 \text{ \AA}$ and $150^\circ < \theta < 180^\circ$), but it seems hard to imagine that these interactions do not determine the packing of this structure. Surprisingly, not even the C17—H17 \cdots O5 bond succeeds in imposing a planar C17/N4/C20/O5/O6/C21 group, although such a conformation has been observed, for example, in 11-methoxy-15,16-dihydroxycyclopenta[*a*]phenanthren-17-one (Desiraju *et al.*, 1993). The steric factor warping the aza-propane and aminocarboxylate groups is finally demonstrated by the asymmetry of the C22—H22 \cdots O5 and C24—H24 \cdots O5 bonds and by the C23—C21—O6—C20 torsion angle of $-167.88(18)^\circ$.

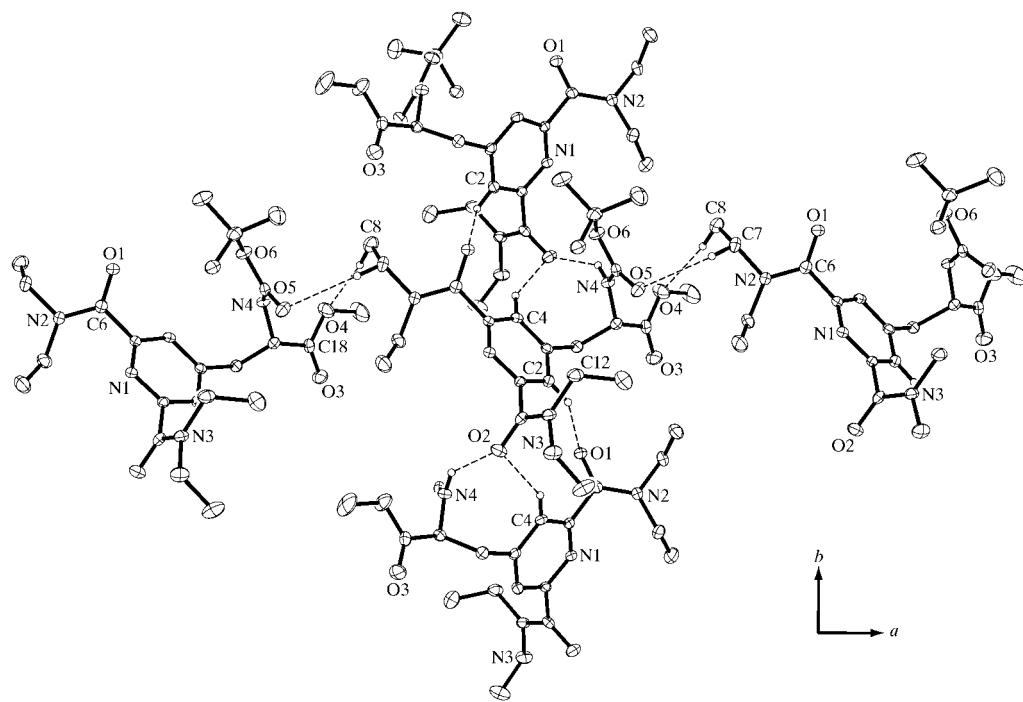


Figure 2

Hydrogen bonds in one of the *ab* layers. The layer-connecting hydrogen bonds involve O3.

The average bond lengths fall well within the ranges listed in the *International Tables for Crystallography* (1992, Vol. C). Following the example of Desiraju (1996), normalized N–H and C–H distances were used for the compilation of Table 1, although the refined distances reached satisfactory values, for example, 1.004 Å for the mean C–H bond. Despite the presence of several O and N atoms and the good quality of the data, the structure does not possess an enantiomorph-discriminating capacity that is high enough to furnish the absolute configuration of atom C17. However, since the synthesis involved no chirality-inverting step, atoms C17a and C17b are likely to be *S*.

The structure shows that the *trans-trans* configuration of atoms O1 and O2 prevails in the solid state. This configuration is probably due to a minimization of the steric repulsion of the two carbamate groups, and the chiral substituent grafted onto the 4-position of the pyridine ring. During complexation, this configuration changes to *cis-cis*.

On the other hand, chiro-optical data clearly suggest the helical wrapping of the three ligand strands around the Ln^{III} ions. This fact is confirmed by specific rotary dispersion measurements (Muller, Schmidt *et al.*, 2001) but is contrary to the situation observed when bulky neopentyl substituents were grafted onto the benzimidazole sidearms of a 2,6-bis(1-*S*-neopentylbenzimidazol-2-yl)pyridine ligand (Muller, Bünzli *et al.*, 2001). Moreover, the circularly polarized luminescence of the Eu^{III} triple helical complex displays a weak effect, pointing to a small diastereomeric excess in solution, similar to that recently observed for the corresponding complex with 2,6-bis(1-methylbenzimidazol-2-yl)-4-(neopentyl ester)pyridine, which also bears a chiral group in the 4-position of the central pyridine ring (Muller *et al.*, 2002). Therefore, the diastereomeric induction resulting from the influence of the helical wrapping may be modulated by varying the chiral substituent in the 4-position of the pyridine ring, as may the electronic and photophysical properties. The combination of these properties opens new perspectives for the design of lanthanide triple helical complexes acting as probes for chiral recognition.

Experimental

Ligand L⁴ was synthesized from 4-bromo-*N,N,N',N'*-tetraethylpyridine-2,6-dicarboxamide *via* a palladium-mediated reaction with Jackson's zinc reagent (yield 61%). The details of the preparation have been described elsewhere (Muller, Schmidt *et al.*, 2001). The yellow solid was recrystallized, by slow diffusion of hexane into a dichloromethane solution, to yield [010] joists. The habitus of the measured cut consisted of the {101} prism, the {100} pinacoid and the (010)/(010) cut planes.

Crystal data

$C_{24}H_{38}N_4O_6$	$D_x = 1.199 \text{ Mg m}^{-3}$
$M_r = 478.58$	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 8000 reflections
$a = 11.144 (2) \text{ \AA}$	$\theta = 13.8\text{--}28.0^\circ$
$b = 13.047 (3) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$c = 18.429 (4) \text{ \AA}$	$T = 115 (2) \text{ K}$
$\beta = 98.19 (3)^\circ$	Prism, yellow
$V = 2652.2 (10) \text{ \AA}^3$	$0.40 \times 0.40 \times 0.15 \text{ mm}$
$Z = 4$	

Table 1
Hydrogen-bonding geometry (Å, °).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
C2–H2a···O1 ⁱ	1.08	2.42	3.234 (3)	131
N4–H4a···O2 ⁱⁱ	1.01	2.05	2.899 (2)	140
C4–H4b···O2 ⁱⁱ	1.08	2.45	3.391 (3)	145
C12a–H12c···O3 ⁱⁱⁱ	1.06	2.56	3.350 (3)	131
C8–H8b···O4 ^{iv}	1.06	2.46	3.504 (3)	169
C7–H7b···O5 ^{iv}	1.06	2.47	3.428 (3)	151
C9–H9a···N1	1.06	2.56	3.041 (3)	107
C17–H17a···O5	1.06	2.32	2.802 (2)	106
C22–H22c···O5	1.06	2.33	2.917 (3)	113
C24–H24a···O5	1.06	2.53	3.123 (3)	114
C2a–H2aa···O1a ^v	1.08	2.24	3.131 (3)	138
N4a–H4ab···O2a ^{vi}	1.01	2.10	2.949 (2)	141
C8a–H8ab···O4a ^{iv}	1.06	2.39	3.451 (3)	180
C9a–H9aa···N1a	1.06	2.56	3.021 (3)	106
C17a–H17b···O5a	1.06	2.29	2.784 (2)	107
C22a–H22f···O5a	1.06	2.39	2.971 (3)	113
C24a–H24d···O5a	1.06	2.42	3.032 (3)	116

Symmetry codes: (i) $-x, y - \frac{1}{2}, 1 - z$; (ii) $-x, \frac{1}{2} + y, 1 - z$; (iii) $x, y, 1 + z$; (iv) $x - 1, y, z$; (v) $-x, y - \frac{1}{2}, 2 - z$; (vi) $-x, \frac{1}{2} + y, 2 - z$.

Table 2
Selected geometric parameters (Å, °).

O1–C6	1.229 (3)	O6–C20	1.343 (3)
O2–C11	1.239 (3)	N2–C6	1.350 (2)
O3–C18	1.199 (3)	N3–C11	1.340 (2)
O4–C19	1.454 (3)	N4–C20	1.357 (3)
O5–C20	1.220 (3)	C2–C3	1.387 (3)
O1–C6–N2		123.29 (19)	O5–C20–N4
O2–C11–N3		123.1 (2)	124.5 (2)

Data collection

Stoe IPDS diffractometer
 φ scans
38 694 measured reflections
6220 independent reflections
5570 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.045$

H-atom parameters constrained
 $(\Delta/\sigma)_{\text{max}} = 0.001$
 $\Delta\rho_{\text{max}} = 0.24 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.20 \text{ e \AA}^{-3}$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.035$
 $wR(F^2) = 0.057$
 $S = 2.90$
6220 reflections
663 parameters

The χ^2 value of 2.90 calls for an explanation. Indeed, a δR_{exp} versus δR_{stat} NPP displays a slope of 1.9 and a δR_{exp} axis intercept of 0.09. The line is perfectly straight (except in the tails), suggesting that the experimental s.u. values have been underestimated (a common observation in single-crystal diffraction experiments) rather than that the data are suspicious. All the other usual plots and the small number of inconsistent equivalents (70) confirm the sound nature of this data collection. The number of reflections is 291 short of completeness; these were overloaded reflections that could, unfortunately, not be remeasured because of technical problems. Friedel pairs were averaged. H atoms were placed in calculated positions and refined using a riding model with variable C–H distances. Anisotropic displacement parameters were preferred for all non-H atoms.

Data collection: *IPDS Software Package* (Stoe & Cie, 1997); cell refinement: *IPDS Software Package*; data reduction: *IPDS Software Package*; program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1996); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1603). Services for accessing these data are described at the back of the journal.

References

- Abrahams, S. C. & Keve, E. T. (1971). *Acta Cryst. A* **27**, 157–165.
Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Burla, M. C., Polidori, G., Camalli, M. & Spagna, R. (1997). *SIR97*. University of Bari, Italy.
- Bruker (1996). *SHELXTL*. Version 5.05. Bruker AXS Inc., Madison, Wisconsin, USA.
Desiraju, G. R. (1996). *Acc. Chem. Res.* **29**, 441–449.
Desiraju, G. R., Kashino, S., Coombs, M. M. & Glusker, J. P. (1993). *Acta Cryst. B* **49**, 880–892.
Govenlock, L. J., Mathieu, C. E., Maupin, C. L., Parker, D., Riehl, J. P., Siligardi, G. & Williams, J. A. G. (1999). *Chem. Commun.* pp. 1699–1700.
Guo, Z. J. & Sadler, P. J. (1999). *Angew. Chem. Int. Ed.* **38**, 1512–1531.
Muller, G., Bünzli, J.-C. G., Schenk, K. J., Piguet, C. & Hopfgartner, G. (2001). *Inorg. Chem.* **40**, 2642–2651.
Muller, G., Riehl, J. P., Schenk, K. J., Hopfgartner, G., Piguet, C. & Bünzli, J.-C. G. (2002). *Eur. J. Inorg. Chem.* pp. 3101–3110.
Muller, G., Schmidt, B., Jiříček, J., Hopfgartner, G., Riehl, J. P., Bünzli, J.-C. G. & Piguet, C. (2001). *J. Chem. Soc. Dalton Trans.* pp. 2655–2662.
Parker, D. (2000). *Coord. Chem. Rev.* **205**, 109–130.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Stoe & Cie (1997). *IPDS Software Package*. Version 2.89. Stoe & Cie GmbH, Darmstadt, Germany.
Tsukube, H. & Shinoda, S. (2002). *Chem. Rev.* **102**, 2389–2403.
Yam, V. W.-W. & Lo, K. K.-W. (1999). *Coord. Chem. Rev.* **184**, 157–240.