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An isoindoline EPR label: 5-acetamido-1,1,3,3-tetramethylisoindolin-2-yloxyl

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Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.007 Å
R factor = 0.039
wR factor = 0.125
Data-to-parameter ratio = 7.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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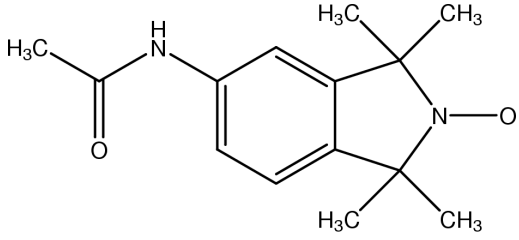
The crystal structure of the isoindoline nitroxide amide 5-acetamido-1,1,3,3-tetramethylisoindolin-2-yloxyl, $C_{14}H_{19}N_2O_2$, which has utility as an EPR label, shows a characteristically stable tetramethyl-substituted nitroxide ring system which is essentially coplanar with the amide side-chain substituent. A single intermolecular hydrogen bond between the amide H atom and the nitroxide O atom links the molecules head-to-tail into an infinite polymeric chain.

Comment

Nitroxides are often utilized as reporter molecules and, as such, are commonly referred to as spin labels or spin probes depending upon whether they are covalently linked (labels), or not (probes), to the system being studied. Precise knowledge of the bonding structure of spin labels is essential to obtain information on complex systems such as enzymes and other macromolecules (Farrens *et al.*, 1996; Steinhoff *et al.*, 1997; Rink *et al.*, 1997; Mchaourab *et al.*, 1997). Another crucial issue in the utilization of stable nitroxide probes in biological systems is the partitioning behaviour which governs membrane transfer. Charged nitroxides generally do not cross cell membranes, although there are exceptions (Kocherginsky & Swartz, 1995) and amphiphilic nitroxides may orient themselves with the non-polar portion of the molecule embedded in the lipid bilayer. Lipophilic nitroxides have also been associated with enhanced cytotoxicity, albeit in high concentrations (> 1 m*M*). We have synthesized (Reid *et al.*, 1998) amino substituted isoindoline nitroxides as potential new EPR spin labels/probes and in order to contrast the toxicity and partitioning preferences, have now synthesized the novel 5-acetamido-1,1,3,3-tetramethylisoindolin-2-yloxyl, (I), reported here.



(I)

Single-crystal X-ray analysis of the structure of this amide (Fig. 1) provides insight into the bonding characteristics resulting when this type of EPR label is bound to an amino acid sequence. This reveals a basic tetramethylisoindoline core which is relatively inflexible and therefore similar to the

previously reported compounds of the same type (Micallef *et al.*, 1999). The N8—O8 bond distance [1.279 (5) Å] compares closely with these examples. The amide side chain adopts a conformation such that it is almost coplanar with the parent aromatic ring system [torsion angles C4—C3—N31—C31 172.9 (5)° and C3—N31—C31—O31 −5.5 (9)°]. This is stabilized by the presence of an intramolecular hydrogen bond between the amide-O and a ring-H atom [O31···H2—C2 2.880 (7) Å]. A single head-to-tail hydrogen bond between the amide group and the nitroxide O atom [N31—H31···O8^{i} 2.884 (7) Å and N—H···O, 171 (3)°] [symmetry code: (i) $-\frac{1}{2}+x$, $\frac{3}{2}-y$, $-\frac{1}{2}+z$] links the molecules into an infinite poymeric chain.

Experimental

The title compound was prepared according to the method of Reid *et al.* (1998), by reacting 5-amino-1,1,3,3-tetramethylisoindolin-2-yloxyl in tetrahydrafuran containing 1.5 equivalents of sodium bicarbonate, with 10 equivalents of acetyl chloride. Extraction into diethyl ether and recrystallization from acetonitrile gave data quality crystals.

Crystal data

$C_{14}H_{19}N_2O_2$
M_r = 247.32
Monoclinic, *Cc*
a = 14.325 (4) Å
b = 8.536 (8) Å
c = 11.513 (4) Å
β = 91.56 (2)°
V = 1407 (1) Å^3
Z = 4
D_x = 1.167 Mg m^{-3}
Mo Kα radiation
Cell parameters from 25 reflections
θ = 10.4–16.3°
μ = 0.08 mm^{-1}
T = 295 K
Block, yellow
0.38 × 0.28 × 0.15 mm

Data collection

Rigaku AFC-7*R* diffractometer
ω–2θ scans
1384 measured reflections
1286 independent reflections
716 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 25.0°
$h = 0 \rightarrow 16$
$k = 0 \rightarrow 10$
$l = -13 \rightarrow 13$
3 standard reflections
every 150 reflections
intensity decay: 2.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.125
S = 1.03
1286 reflections
164 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0598P)^2 + 0.1927P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.007
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0023 (2)

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1999*a*); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN for Windows* (Molecular Structure Corporation, 1999*b*); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); software used to prepare material for publication: *TEXSAN* for Windows (Molecular Structure Corporation, 1999*b*) and *PLATON for Windows* (Spek, 1999).

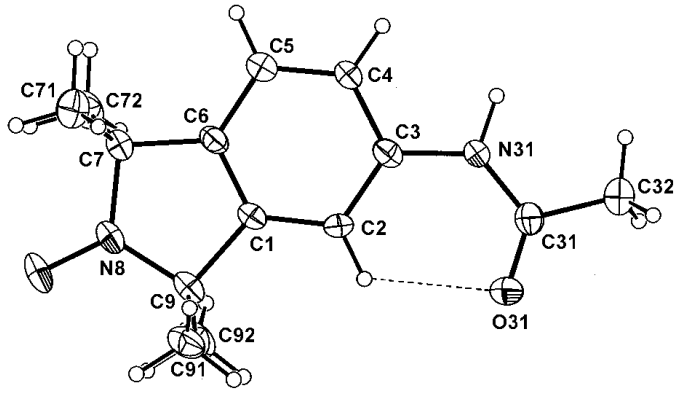


Figure 1
The molecular conformation and atom-naming scheme with the atoms shown as 30% probability ellipsoids (Spek, 1999).

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