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Hydrogen Bonding Patterns in a Series of 3-Spirocyclic Oxindoles

Andreas Lemmerer* and Joseph P. Michael

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg, P.O. WITS 2050, South Africa.

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ABSTRACT

The crystal structures of the new compounds spiro[cyclohexane-1,3′-indol]-2′(1′*H*)-one (1), (*rel*-1*R*,2*S*)-spiro[bicyclo[2.2.1]heptane-2,3′-indol]-2′(1′*H*)-one (2) and spiro[indole-3,2′-tricyclo[3.3.1.1^{3,7}]decan]-2(1*H*)-one (3) have been determined by low temperature single crystal X-ray diffraction. The effects of substitution on the hydrogen bonding pattern is compared between all three compounds.

KEYWORDS

Hydrogen bonding, X-ray crystal structure, oxindoles, Cambridge Structural Database.

1. Introduction

Oxindoles (1,3-dihydroindol-2(1*H*)-ones) bearing spirocyclic substituents at C-3 are well represented in nature. These substructures are common in alkaloids isolated from the plant genera *Gelsemium,*[1] *Mitragyna*[2] and *Uncaria,*[3] among others,[4] as well as in various natural products isolated from microorganisms, including *Penicillium.*[5,6,7,8] Several recent reviews have been devoted to the total synthesis of such oxindole alkaloids.[9,10,11] Over two decades ago we reported novel synthetic routes to the 3-spirocyclic oxindoles **1**–**3**,[12,13] which were intended to serve as models in the development of methodology aimed at the total synthesis of gelsemine **4**, a complex spiro-oxindole alkaloid.[14]

We previously reported substituent effects on crystal packing in a series of 1-arylcarboxamides.[15] The primary hydrogen bonded interaction observed in the five compounds was a homomeric carboxamide cyclic dimer, having Graph Set Notation $R_2^2(8)$.[16] The formation of this supramolecular homosynthon **I** (Scheme 1) is well documented, as in the 1312 structures (See supplementary information S1 for details of search query) in the Cambridge Structural Database (CSD) that contain it, 518 form dimers (43.3 %) (S2 contains the list of entries).[17] The same carboxamide can also form chains, homosynthon **II**, and is the second most observed motif, shown in 441 structures (36.8 %) (listed in S3).[17] In the compounds used in this study, the functional group with hydrogen bonding capability is closely related to the generic carboxamide, with the *anti*-H replaced by a carbon atom. For this functionality, there are a total of 10890 structures in the CSD and there are 1685 (15.5 %) dimers (listed in S4) and 2406 (23.9 %) chains (listed in S5).[18] By changing the substituent at the 3-position of the oxindole backbone, we can observe its effect on the crystal structures and packing modes of compounds **1**–**3** (Scheme 2).

* To whom correspondence should be addressed. E-mail: andreas.lemmerer@wits.ac.za

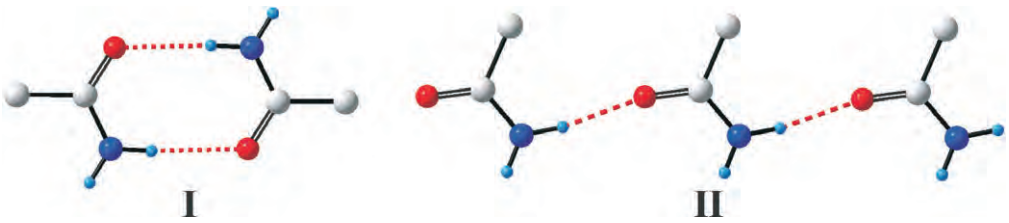
2. Experimental

2.1. Materials

Compounds **1**–**3** were prepared as described previously.[13] Crystals of **1** were grown from hexane–ethyl acetate, **2** from ethanol and **3** from benzene, by slow evaporation.

2.2. X-ray Crystallography

A summary of the crystallographic data is given in Table 1. Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA, $\lambda = 71073$ Å). The collection method involved ω-scans of width 0.3 °. Data reduction was carried out using the program *SAINT+*, version 6.02[19] and face indexed absorption corrections were made using the program *XPREP.*[19] The crystal structure was solved by direct methods using *SHELXS-97.*[20] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXL-97.*[20] H atoms on C atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. H atoms on N atoms that are involved in hydrogen bonding interactions in **1**, **2** and **3** were located in the difference map and their positions allowed to refine freely. All hydrogen atoms have their isotropic thermal parameters assigned as 1.2 times those of their parent atoms. Diagrams and publication material were generated using *WinGX,*[21] *ORTEP,*[22] *PLATON*[23] and *DIAMOND.*[24] CCDC-724730

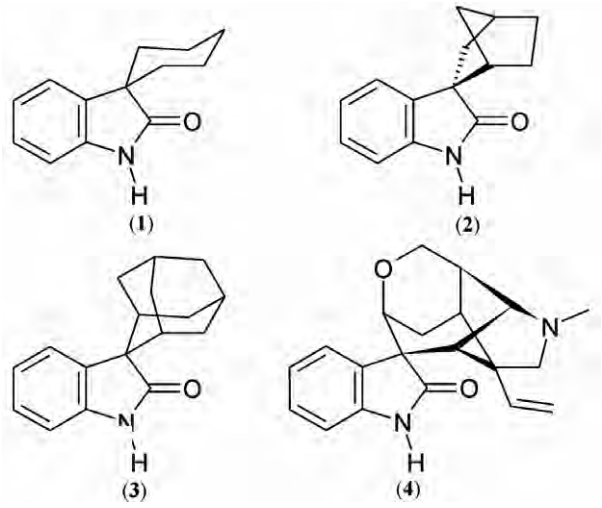


Scheme 1
The common hydrogen bonding synthons **I** and **II** observed in carboxamides and observed in the spiro-oxindoles in this study.

Table 1 Summary of structure determination of compounds **1, 2, 3** and **4**.

Compound	**1**	**2**	**3**
CCDC entry no.	724730	724731	724733
Empirical formula	$C_{13}H_{15}NO$	$C_{14}H_{15}NO$	$C_{20}H_{22}NO$
M_r/g mol^{-1}	201.26	213.27	292.39
T/K	173	173	173
Crystal system	orthorhombic	monoclinic	triclinic
Space group	*P*bcn	$P2_1/c$	$P\bar{1}$
a/Å	16.843(7)	10.1725(11)	9.7069(2)
b/Å	9.049(4)	8.8556(9)	9.8576(2)
c/Å	14.337(6)	12.9533(12)	9.9415(2)
α/°	90	90	67.369(1)
β/°	90	111.162(6)	81.989(1)
γ/°	90	90	60.864(1)
V/Å^3	2185.1(15)	1088.19(19)	765.57(3)
Z	8	4	2
μ/mm^{-1}	0.077	0.082	0.077
Absorption correction	Face-indexed	Face-indexed	Face-indexed
Max, min transmission	0.9869, 0.9473	0.9842, 0.9584	0.9883, 0.9582
F(000)	864	456	314
Crystal size/mm	0.60 × 0.60 × 0.16	0.60 × 0.44 × 0.20	0.36 × 0.32 × 0.25
θ range for data collection/°	2.42–28.00	2.15–28.00	2.22–28.00
Reflections collected	18345	10071	12994
Unique data [R(int)]	2639 [0.0537]	2625 [0.0611]	3674 [0.0394]
No. data with $I \geq 2\sigma(I)$	2150	2144	3143
Goodness-of-fit on F^2	1.046	0.930	1.053
R_1 [$I > 2\sigma(I)$], R_1 [all data]	0.0411, 0.0514	0.0432, 0.0541	0.0421, 0.0480
wR_2 [$I > 2\sigma(I)$], wR_2 [all data]	0.1066, 0.1126	0.1126, 0.1189	0.1141, 0.1185
Largest peak/hole (eÅ^{-3})	0.261/–0.210	0.309/–0.226	0.297/–0.257

(**1**), 724731 (**2**) and 7247333 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.ul/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk].



Scheme 2
Spiro-oxindoles **1**–**3** investigated in this study, and gelsemine **4**.

3. Results and Discussion

3.1. Crystallographic Descriptions of the Structures of the Spiro-oxindoles 1–3

Table 1 provides crystallographic details for compounds **1–3.** The atomic numbering scheme for all three compounds is given in Fig. 1, which also shows the contents of the asymmetric unit in each case. The distances and angles within the three compounds reported are generally as expected.[25] In all three structures, hydrogen bonds (summarized in Table 2) play a part in controlling the supramolecular assembly of the molecules. In describing the hydrogen-bonding patterns in the three spiro-oxindole structures reported in this study, we shall use unitary (N_1) graph set (GS) analysis.[16] Furthermore, weak C–H$\cdots\pi$ interaction are also present in **2** and **3**, which are summarized in Table 3.

The compound spiro[cyclohexane-1,3′-indol]-2′(1′*H*)-one (**1**) crystallized in the space group *P*bcn with one molecule in the asymmetric unit ($Z' = 1$). The structure contains one unique hydrogen bond. The N1–H1$\cdots$O1 hydrogen bond forms $R_2^2(8)$ dimers. The unitary GS notation is $N_1 = R_2^2(8)$. The dimers pack in a herringbone fashion along the *a*-axis (Fig. 2).

The structure of (*rel*-1*R*,2*S*)-spiro[bicyclo[2.2.1]heptane-2,3′-indol]-2′(1′*H*)-one (**2**) has one molecule in the asymmetric unit ($Z' = 1$). The crystal system is monoclinic, and the compound crystallized in the centrosymmetric space group type $P2_1/c$. The N1–H1…O1) hydrogen bond forms chains of

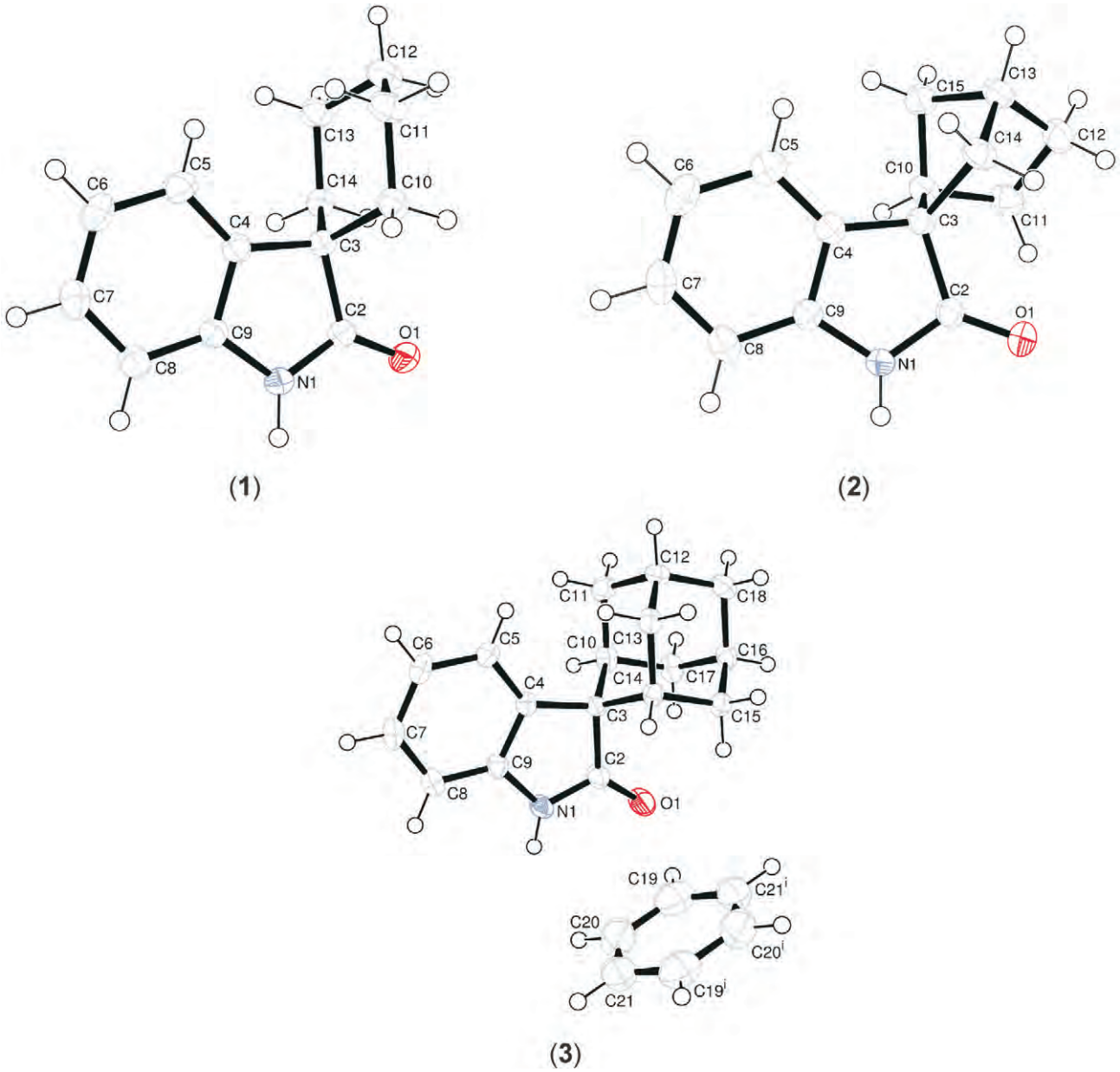


Figure 1 The molecular structures of **1–3** showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50 % probability level and hydrogen atoms are drawn as small spheres of arbitrary radii. Atoms marked with superscript [i] are at the symmetry position (1–*x*, –*y*, –*z*).

hydrogen bonded molecules, linked along the *b*-axis. The GS notation for this motif is $N_1 = C(4)$. The hydrogen bonded chains are linked to adjacent chains by weak C–H···π interactions, with atom C15 interacting with the centroid Cg1 of the aromatic group C4–C9 through atom H15B (Fig. 3).

The structure of **3** has one spiro[indole-3,2′-tricyclo-[3.3.1.1^{3,7}]decan]-2(1*H*)-one molecule in the asymmetric unit ($Z' = 1$) and half a benzene solvent molecule in the asymmetric unit. The crystal system is triclinic, and the compound crystallized in the centrosymmetric space group type $P\bar{1}$. The N1–H1···O1 hydrogen bond forms dimers of hydrogen bonded molecules, linked along the *b*-axis. The GS notation for this motif

Table 2 Hydrogen bonding interactions for all compounds.

D-H···A	d(D-H)/Å	d(H···A)/Å	d(D···A)/Å	<(DHA)/°
1				
N1-H1···O1^{i}	0.92(1)	1.94(2)	2.846(2)	170(1)
2				
N1-H1···O1^{ii}	0.86(2)	2.09(2)	2.863(1)	149(1)
3				
N1-H1···O1^{iii}	0.89(2)	1.93(2)	2.818(1)	175(1)

[Symmetry operators: (i) –x + 1, –y, –z + 1; (ii) –x + 1, y – 1/2, –z + 3/2; (iii) –x + 1, –y, –z + 1]

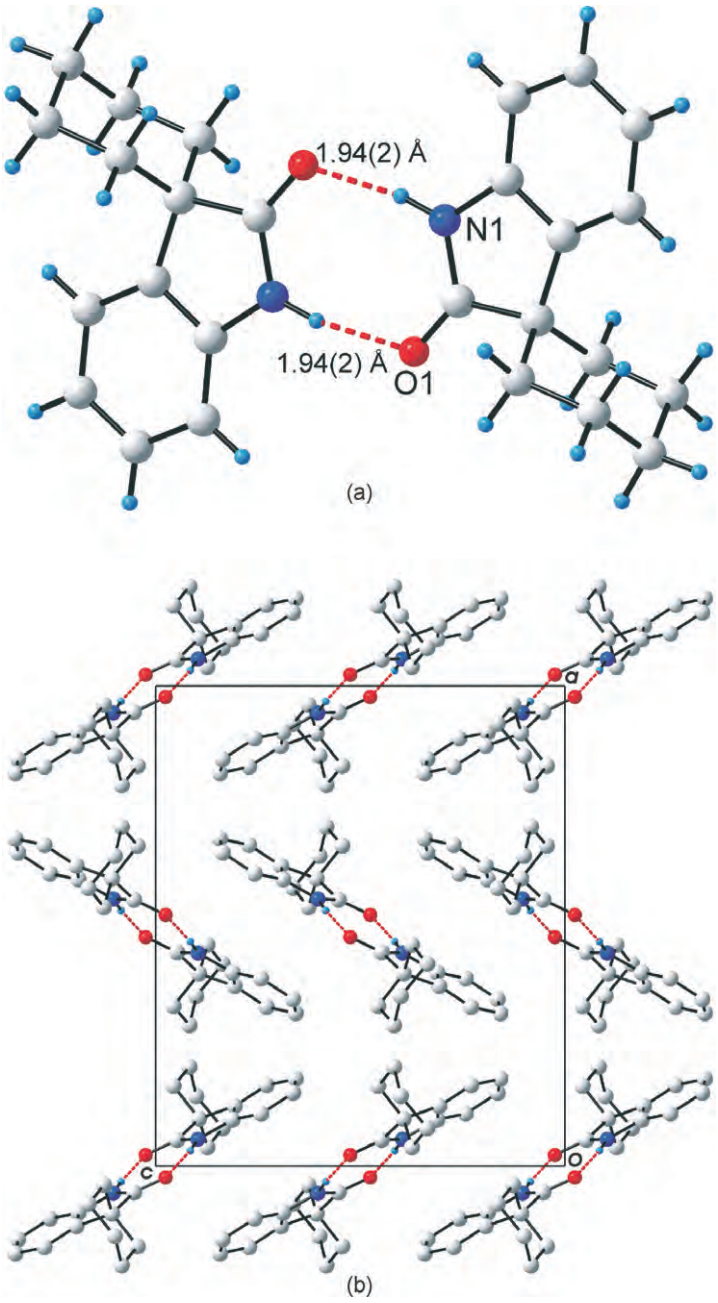


Figure 2 (**a**) The hydrogen bonded dimer of **1;** (**b**) packing diagram viewed down the *b*-axis.

is $N_1 = R_2^2(8)$. The hydrogen bonded dimers are linked to adjacent dimers by weak C–H···π interactions, with atom C13 interacting with the centroid *Cg*1 of the aromatic group C4–C9 through atom H13B. The C13–H13B···*Cg*1 interaction forms dimers as well. There are no intermolecular interactions to the solvent benzene ring and the crystals decompose rapidly once removed from the mother liquor. Incidentally, when the compound was recrystallized from acetone, the poorly resolved structure (not reported) displayed essentially the same packing mode as shown in Fig. 4, with the solvent occupying the same interstices in the lattice as benzene.

3.2. Comparison of Structures 1–3

Before one can make any deductions on the substituent effects

Table 3 C-H···π geometries.

C-H···*Cg*	d(C-H)/Å	d(H···*Cg*)/Å	d(C···*Cg*)/Å	<(CH*Cg*)/^{0}
2				
C15-H15B···*Cg*1^{i}	0.99	2.93	3.905(2)	168
3				
C13-H13B···*Cg*1^{ii}	0.99	2.78	3.639(1)	145

[Symmetry operators: (i) $-x + 2, y + 1/2, -z + 3/2$; (ii) $-x + 1, -y + 1, -z$]

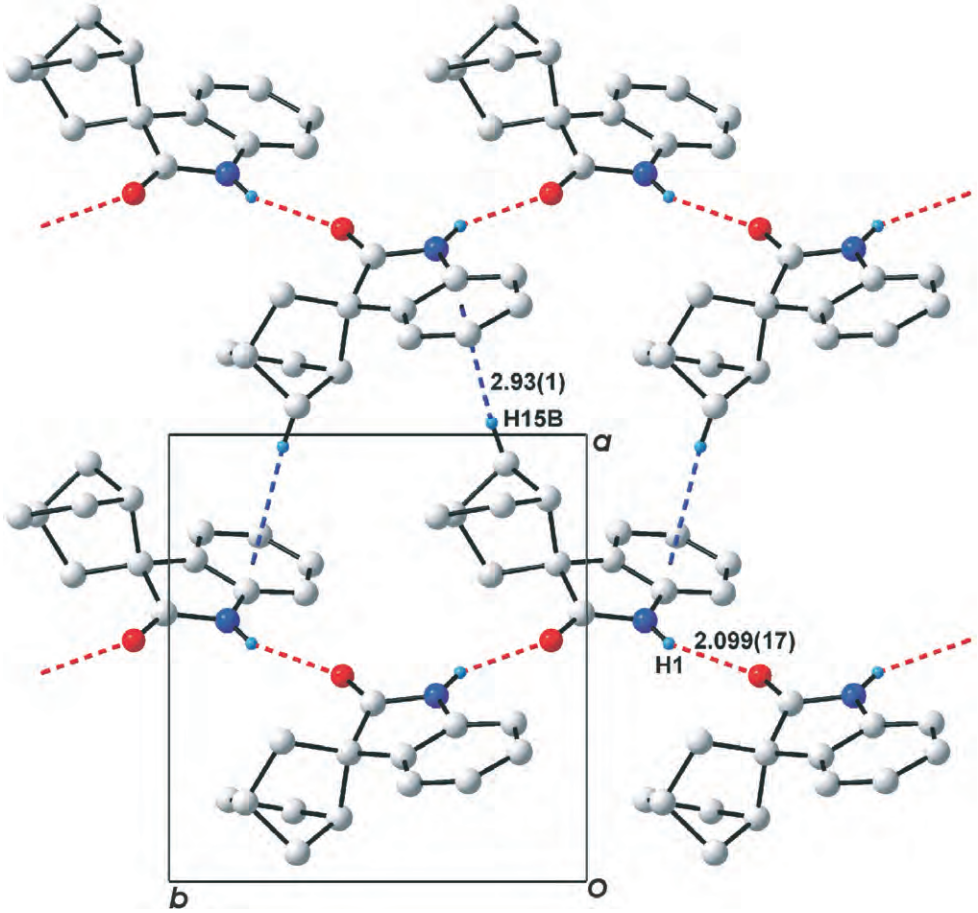


Figure 3 Packing diagram of **2** showing how adjacent *C*(4) hydrogen bonded chains (dashed red lines) running along the *b*-axis are linked along the *a*-axis by C-H···π interactions (dashed blue lines).

on C-3 on the packing of the four reported compounds, one can use the CSD to analyse the percentage occurrence of dimers, chains and other motifs that can be formed from the oxindole parent backbone. We found 135 structures reported in the CSD.[26] Of these, 61 form dimers (45.5 %) (listed in S7), 17 form chains (12.7 %) (listed in S8) and 56 form other motifs. Structure **1**, with a cyclohexane substituent, forms the generic $R_2^2(8)$ dimer, which then becomes a chain motif when the substituent is the chiral spiro group as in **2**. The carbonyl group occupies the sterically hindered *endo* position of the norbornyl system; that might conceivably inhibit the formation of the cyclic dimers. The N–H···O hydrogen bond in **3** reverts back to a ring motif. A possible reason for **3** containing a solvent molecule could be due to the large steric size of the adamantane substituent at C-3. The steric bulk of the substituent hinders the close packing of the molecules, resulting in interstitial sites that are filled by the solvent molecule.

4. Conclusions

The single crystal X-ray structures of three spiro-oxindoles spiro[cyclohexane-1,3′-indol]-2′(1′*H*)-one (**1**), (*rel*-1*R*,2*S*)-spiro[bicyclo[2.2.1]heptane-2,3′-indol]-2′(1′*H*)-one (**2**) and spiro[indole-3,2′-tricyclo[3.3.1.1^{3,7}]decan]-2(1*H*)-one (**3**) were determined. The hydrogen bonding motif formed by the N–H···O hydrogen bonds are centrosymmetric dimers in **1** and **3** and infinite chains in **2**.

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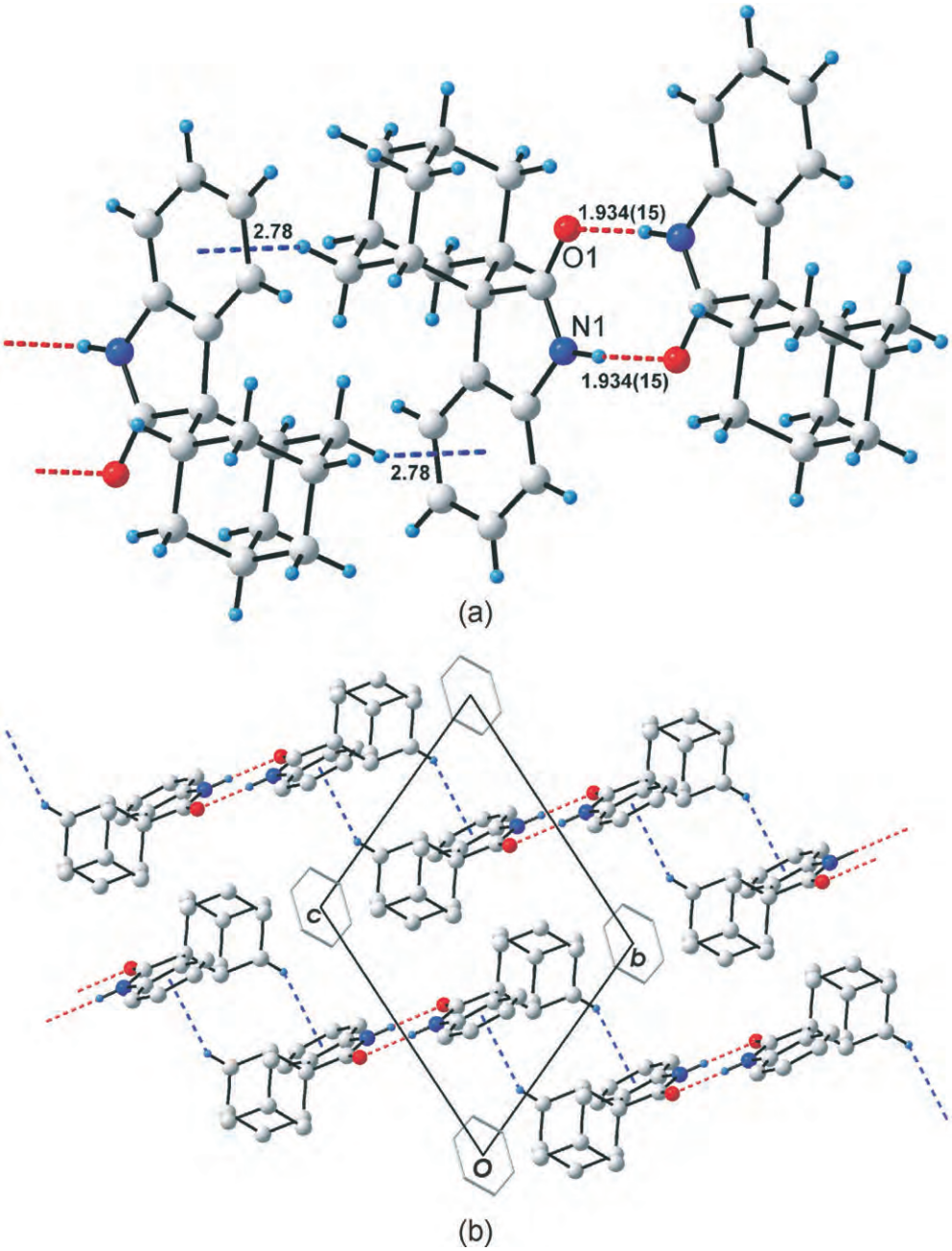

Figure 4 (**a**) The N1–H1···O1 (dashed red lines) and C13-H13B···*Cg*1 (dashed blue lines) dimers of **3**; (**b**) packing diagram of **3**, showing the solvent benzene molecules (wireframe model) located at the inversion centres in *P*–1.

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26 Search Query: Molecular fragment oxindole backbone, any substituents on the 3-position. Filters: 3D coordinates determined, *R* factor ≤ 0.075, not disordered, no errors, no ions, no powder structures, only organics. 167 hits which was reduced to 135 by manually removing duplicate entries, entries containing solvent molecules, and those containing no H atom coordinates.