

The Knoevenagel product of indolin-2-one and ferrocene-1,1'-dicarbaldehyde

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Received 21 January 2011

Accepted 3 June 2011

Online 25 June 2011

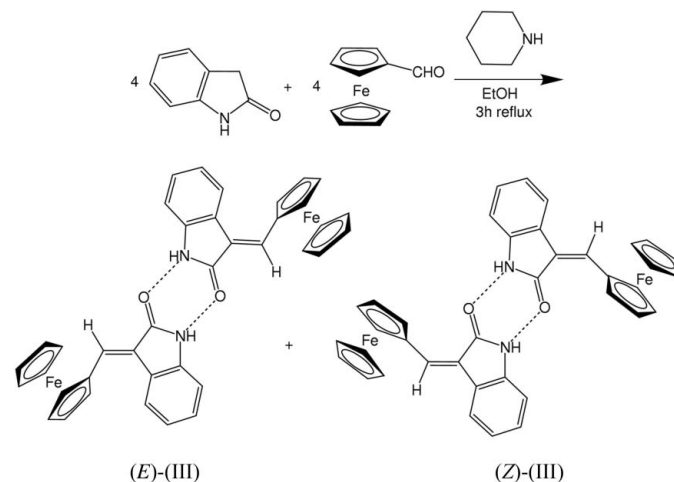
Indolin-2-one (oxindole), (I), undergoes a Knoevenagel condensation with ferrocene-1,1'-dicarbaldehyde, (II), to afford the title complex 3,3'-[(*E,E*)-ferrocene-1,1'-diyldimethylidene]diindolin-2-one dichloromethane disolvate, [Fe(C₂₈H₂₀N₂O₂)]·2CH₂Cl₂, (IV). The structure of (IV) contains two ferrocene complex molecules in the asymmetric unit and displays, as expected, intermolecular hydrogen bonding (N—H...O=C) between the indolin-2-one units. Intermolecular π–π stacking interactions are also observed.

Comment

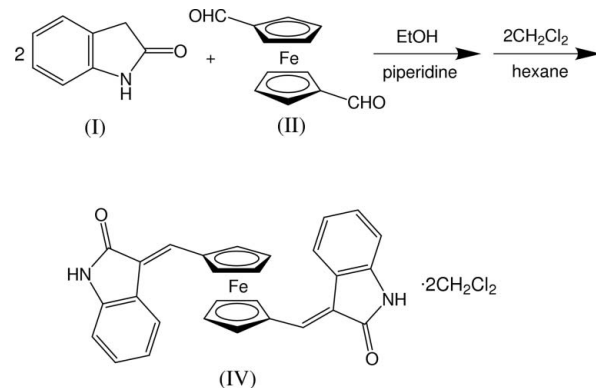
The chemistry of ferrocenes continues to flourish (van Staveren & Metzler-Nolte, 2004; Ren, 2008; Diallo *et al.*, 2009, and references therein) and spans a plethora of disciplines, including medicinal chemistry (Dubar *et al.*, 2008; Auzias *et al.*, 2009; Higgins & Gellett, 2009), catalysis (Togni & Hayashi, 1995), novel materials (Shoji *et al.*, 2009), sensors (Oton *et al.*, 2006; Qing *et al.*, 2009), supramolecular chemistry (Tan *et al.*, 2008) and the design of extended molecular architectures, which often exploit intra- or intermolecular hydrogen bonding (Stepnicka *et al.*, 2008; Hirao, 2009, and references therein; Lataifeh *et al.*, 2009). We and others have recently published the synthesis of the isomeric ferrocenyl oxindoles, (*E*)- and (*Z*)-3-(ferrocenylmethylidene)indolin-2-one, denoted (*E*)- and (*Z*)-(III), which are readily separated and have excellent anticancer properties (see scheme). We have shown that (*E*)- and (*Z*)-(III) display intermolecular NH...O=C hydrogen bonding in the solid state (Silva *et al.*, 2008; Spencer *et al.*, 2009).

To extend the hydrogen-bond capability of related systems, we have now reacted (I) with ferrocene-1,1'-dicarbaldehyde, (II), with a view to synthesizing ferrocene-1,1'-diyl oxindoles

(see scheme; Connell *et al.*, 2009). Analysis of the reaction mixture by ¹H NMR spectroscopy revealed a complex spectroscopic pattern, indicating fluxionality or a mixture of isomers (see *Experimental*). Single crystals suitable for X-ray crystallographic analysis were obtained from a solution in dichloromethane–hexane and the structure of the remarkable title complex, (IV), was determined (Figs. 1 and 2). Analysis of



the single crystals by ¹H NMR spectroscopy gave a similar complex spectrum to that of the reaction mixture and thin-layer chromatographic analysis revealed one spot, distinct from either the starting aldehyde or oxindole.



The crystal structure of (IV) contains two crystallographically independent ferrocene complex molecules with two molecules of dichloromethane per molecule (Fig. 1). Of interest, three of a set of seven substituted 3-methylidene-indolin-2-ones (Spencer *et al.*, 2010) and one of the two isomeric ferrocenyl oxindoles (Spencer *et al.*, 2009) previously reported by us also have *Z'* > 1. The geometry of both crystallographically independent ferrocene species in (IV) are comparable with the ferrocenyl oxindoles and substituted oxindoles previously reported by us and others (Silva *et al.*, 2008; Spencer *et al.*, 2009, 2010) and with fragments found in a search of the Cambridge Structural Database (CSD, Version 5.32; Allen, 2002). All four oxindole units in (IV) exist as the (*E*)-isomers, with the average of the four bond angles C11/C111–C12/C112–C13/C113 and C20/C120–C21/C121–C22/C122 being 118.8 (5)°. This is in excellent agreement with the equivalent bond angles in previously reported (*E*)-isomers

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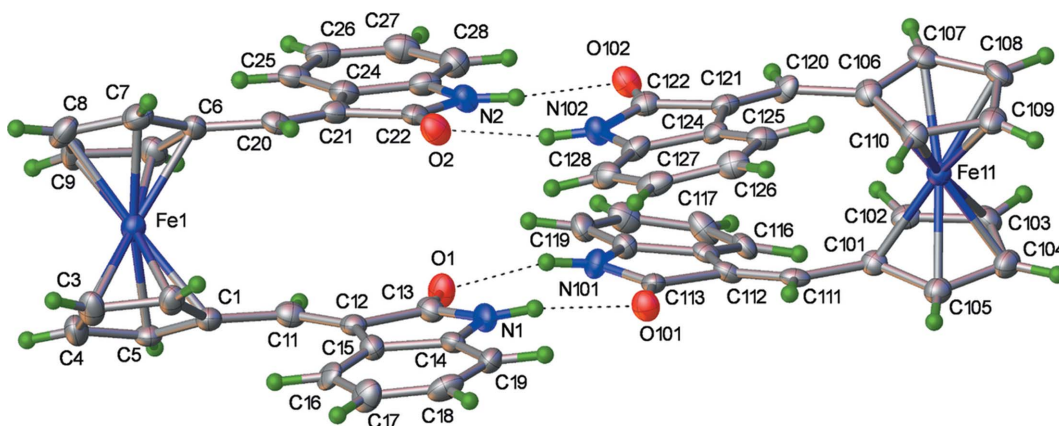


Figure 1
The molecular structure of (IV), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. Dichloromethane solvent molecules have been omitted for clarity. Dashed lines indicate hydrogen bonds.

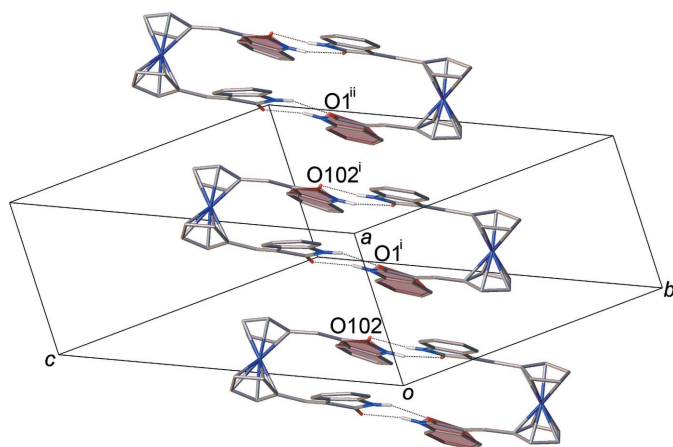


Figure 2
The packing of the hydrogen-bonded dimers (dashed lines) in (IV). Shaded areas indicate the least-squares planes involved in π - π stacking interactions. Dichloromethane solvent molecules have been omitted for clarity and only those H atoms involved in hydrogen bonding are shown. [Symmetry codes: (i) $1 + x, y, z$; (ii) $2 + x, y, z$.]

[averages of $118.5(6)^\circ$ from Spencer *et al.* (2009) and $118.9(2)^\circ$ from Spencer *et al.* (2010)].

While the bond lengths and angles in the two crystallographically independent ferrocene complexes of (IV) are very similar, differences are found in the interplanar distances and angles between the two oxindole units of each complex. The perpendicular separation between the mean plane through oxindole unit O1/N1/C12–C19 and the centroid of oxindole unit O2/N2/C21–C28 is 3.0 \AA , and the angle between the two planes is $4.2(1)^\circ$. The equivalent separation in the other complex molecule, between the mean plane through O101/N101/C112–C119 and the centroid of O102/N102/C121–C128, is a little longer at 3.2 \AA and the angle between the planes is much larger at $15.2(1)^\circ$. The crystallographically independent molecules also show differences in the angles between the planes of the oxindole units and the cyclopentadienyl units to which they are bonded. The angle between the mean plane through O1/N1/C12–C19 and that of the C1–C5 ring is $32.2(2)^\circ$, and that between O2/N2/C21–C28 and C6–C10 is $30.2(2)^\circ$. By contrast, the equivalent angles in the other complex molecule are much smaller, with the angle between O101/N101/C112–C119 and C101–C105 being $22.3(2)^\circ$ and that between O102/N102/C121–C128 and C106–C110 being $19.5(2)^\circ$.

In common with all the previously reported oxindole-based structures (Spencer *et al.*, 2009, 2010), molecular dimers are

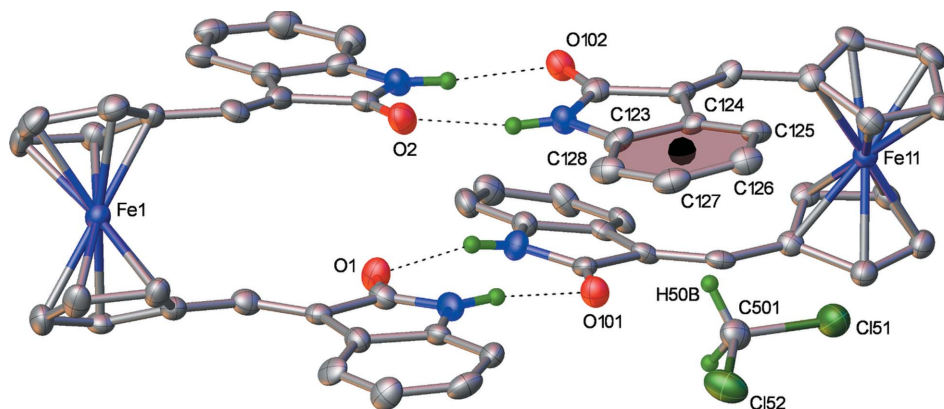


Figure 3
Illustration of the C–H... π (arene) interaction between the C151–C501–C152 dichloromethane group and the C123–C128 benzene ring. The other three dichloromethane solvent molecules and most H atoms have been omitted for clarity. Dashed lines indicate hydrogen bonds.

formed in (IV) through intermolecular N—H···O=C hydrogen bonding. The crystallographically independent molecules form molecular dimers through intermolecular N—H···O=C hydrogen bonding between two pairs of adjacent oxindole units (Figs. 1 and 2, and Table 1). The hydrogen-bonding motif leading to the formation of the molecular dimers can be described as an $R_2^2(8)$ ring (Etter *et al.*, 1990). The dimers are packed into double columns along the [100] direction through π – π stacking interactions (Hunter & Sanders, 1990) between oxindole units N1/O1/C12–C19 and N102/O102/C121–C128, with an interplanar separation of approximately 3.3 Å (Fig. 2).

One of the dichloromethane solvent molecules, C151–C501–C152, forms a short C—H··· π (arene) interaction with the C123–C128 benzene ring (Mocilac *et al.*, 2010) (Fig. 3 and Table 2). In addition, three of the four dichloromethane molecules form weak C—H···Cl or C—H···O interactions with the ferrocene residues (Table 2).

In conclusion, the condensation of ferrocene-1,1'-dicarbaldehyde, (II), with oxindole (I) affords a 1,1'-disubstituted ferrocene, (IV), which displays intermolecular hydrogen bonding (NH···O=C) between two adjacent ferrocenes and four oxindole units. The possibility of engineering further extended hydrogen-bonded networks is currently under investigation in our laboratory.

Experimental

All experiments were conducted in air using reagent-grade solvents, and all chemicals were from commercial sources and used without further purification. CHN elemental analysis was performed on a CE Instruments Eager 300 apparatus. Crystals of (IV) of sufficient quality for X-ray diffraction analysis were obtained by the diffusion of hexane into a CH₂Cl₂ solution.

The synthesis and purification procedure for (IV) were carried out as follows. Oxindole (I) (133 mg, 1 mmol) and ferrocene-1,1'-dicarbaldehyde, (II) (121 mg, 0.5 mmol), were combined in ethanol (10 ml) and piperidine (two drops). The reaction mixture was heated for 3 h at 353 K, cooled and concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (20 ml), washed with brine solution (10 ml) and then dried (MgSO₄). Removal of the MgSO₄ followed by concentration of the solvent afforded an oil, which was taken up in CH₂Cl₂ (5 ml), and a dark-brown precipitate formed upon addition of hexane (20 ml). The precipitate, (IV), was collected by filtration and dried *in vacuo*. Analysis found: C 68.48; H 4.39, N 6.02%; C₂₈H₂₀FeN₂O₂·0.25CH₂Cl₂ requires: C 68.75, H 4.19, N 5.68%. HRMS: *m/z* calculated for C₂₈H₂₀FeN₂O₂·0.25CH₂Cl₂ ($[M + Na \text{ for } ^{56}\text{Fe}]^+$): 493.0815; found: 493.0815. While the empirical formula was found to contain only 0.25 molecules of CH₂Cl₂ per ferrocene complex by elemental analysis and HRMS, the crystal

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

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
N1—H1···O101	0.88	2.01	2.876 (7)	168
N2—H2A···O102	0.88	1.98	2.849 (7)	171
N101—H101···O1	0.88	1.92	2.774 (7)	163
N102—H10A···O2	0.88	1.95	2.822 (7)	169

Table 2

Weak intermolecular interactions in (IV) (Å, °).

Cg1 is the centroid of the C123–C128 benzene ring.

Interaction	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
C201—H20B···O102	0.99	2.64	3.245 (9)	120
C27—H27···C132	0.95	2.87	3.676 (7)	143
C118—H118···C132	0.95	2.91	3.725 (7)	145
C501—H50A···O101	0.99	2.71	3.294 (8)	118
C501—H50B···Cg1	0.99	2.49	3.430 (8)	160

structure was found to contain two molecules of dichloromethane per ferrocene unit. NMR spectra were measured on a JEOL EX270 spectrometer at 270 MHz (1H). ¹H NMR (probably a mixture of isomers): δ 10.49 (1H, *m*), 8.19 (1H, *m*), 7.80 (1H, *m*), 7.38–6.68 (5H, *m*), 5.39 (3H, *m*), 4.96 (2H, *m*), 4.60 (1H, *m*), 4.56 (6H, *m*).

Crystal data

[Fe(C ₂₈ H ₂₀ N ₂ O ₂)]·2CH ₂ Cl ₂	<i>V</i> = 5526.3 (2) Å ³
<i>M_r</i> = 642.16	<i>Z</i> = 8
Monoclinic, <i>P</i> 2 ₁ / <i>c</i>	Mo <i>K</i> α radiation
<i>a</i> = 7.8609 (2) Å	μ = 0.97 mm ^{−1}
<i>b</i> = 14.1905 (4) Å	<i>T</i> = 120 K
<i>c</i> = 49.5413 (12) Å	0.17 × 0.04 × 0.03 mm
β = 90.099 (1)°	

Data collection

Bruker–Nonius APEXII CCD diffractometer	54405 measured reflections
Absorption correction: multi-scan (<i>SADABS</i> ; Sheldrick, 2007)	9612 independent reflections
<i>T</i> _{min} = 0.853, <i>T</i> _{max} = 0.972	7846 reflections with <i>I</i> > 2σ(<i>I</i>)
	<i>R</i> _{int} = 0.063

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.085$	703 parameters
$wR(F^2) = 0.173$	H-atom parameters constrained
<i>S</i> = 1.17	$\Delta\rho_{\text{max}} = 0.63 \text{ e } \text{Å}^{-3}$
9612 reflections	$\Delta\rho_{\text{min}} = -0.55 \text{ e } \text{Å}^{-3}$

All H atoms were added at calculated positions and refined using a riding model, with C—H = 0.95 Å for aromatic or 0.99 Å for methyl-ene groups and N—H = 0.88 Å, and with *U*_{iso}(H) = 1.2*U*_{eq}(C,N).

The *R* factor is rather high, at 0.085. It is thought that this may be the result of the long unit-cell axis (*c* is nearly 50 Å) and the low intensity of the diffraction data, especially at higher 2θ angles. In an effort to deal with these issues, this was the second data set collected on this compound. The data were collected with a molybdenum rotating-anode X-ray source that is approximately ten times more intense than a normal laboratory X-ray source, and the crystal-to-detector distance used was 75 mm, to ensure separation of the reflections. This longer distance obviously led to even lower intensity at the detector. There was no access to a copper X-ray source. To ensure the maximum possible intensity, the data collection was completed in approximately 17 h. The data reduction was carried out carefully to maximize the quality of the data set, but the low intensity of the diffraction at higher angles frustrated these efforts to some degree, leading to the rather high agreement statistics.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolo-

manov *et al.*, 2009); software used to prepare material for publication: *WinGX* (Farrugia, 1999), *Mercury* (Version 2.4; Macrae *et al.*, 2008) and *PARST95* (Nardelli, 1995).

The EPSRC National Mass Spectrometry Unit at the University of Swansea is thanked for mass spectroscopic analysis. The RSC (Research Fund grant), GRE and the University of Greenwich are thanked for financial assistance, and for CHN analysis facilities and the purchase of a Sartorius microbalance.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3253). Services for accessing these data are described at the back of the journal.

References

- Allen, F. H. (2002). *Acta Cryst.* **B58**, 380–388.
- Auzias, M., Gueniat, J., Therrien, B., Süß-Fink, G., Renfrew, A. K. & Dyson, P. J. (2009). *J. Organomet. Chem.* **694**, 855–861.
- Connell, A., Holliman, P. J., Butler, I. R., Male, L., Coles, S. J., Horton, P. N., Hursthouse, M. B., Clegg, W. & Russo, L. (2009). *J. Organomet. Chem.* **694**, 2020–2028.
- Diallo, A. K., Ruiz, J. & Astruc, D. (2009). *Org. Lett.* **11**, 2635–2637.
- Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.
- Dubar, F., Khalife, J., Brocard, J., Dive, D. & Biot, C. (2008). *Molecules*, **13**, 2900–2907.
- Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* **B46**, 256–262.
- Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
- Higgins, P. J. & Gellert, A. M. (2009). *Bioorg. Med. Chem. Lett.* **19**, 1614–1617.
- Hirao, T. (2009). *J. Organomet. Chem.* **694**, 806–811.
- Hunter, C. A. & Sanders, J. K. M. (1990). *J. Am. Chem. Soc.* **112**, 5525–5534.
- Lataifeh, A., Beheshti, S. & Kraatz, H.-B. (2009). *Eur. J. Inorg. Chem.* pp. 3205–3218.
- Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.
- Mocilac, P., Tallon, M., Lough, A. J. & Gallagher, J. F. (2010). *CrystEngComm*, **12**, 3080–3090.
- Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
- Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
- Oton, F., Tarraga, A. & Molina, P. (2006). *Org. Lett.* **8**, 2107–2110.
- Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography, Part A*, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
- Qing, G.-Y., Sun, T.-L., He, Y.-B., Wang, F. & Chen, Z.-H. (2009). *Tetrahedron Asymmetry*, **20**, 575–583.
- Ren, T. (2008). *Chem. Rev.* **108**, 4185–4207.
- Sheldrick, G. M. (2007). *SADABS*. University of Göttingen, Germany.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Shoji, T., Ito, S., Toyota, K. & Morita, N. (2009). *Tetrahedron Lett.* **50**, 2825–2827.
- Silva, B. V., Ribeiro, N. M., Pinto, A. C., Vargas, M. D. & Dias, L. C. (2008). *J. Braz. Chem. Soc.* **19**, 1244–1247.
- Spencer, J., Chowdhry, B. Z., Hamid, S., Mendham, A. P., Male, L., Coles, S. J. & Hursthouse, M. B. (2010). *Acta Cryst.* **C66**, o71–o78.
- Spencer, J., Mendham, A. P., Kotha, A. K., Richardson, S. C. W., Hillard, E., Jaouen, G., Vessières, A., Male, L. & Hursthouse, M. B. (2009). *Dalton Trans.* pp. 918–921.
- Staveren, D. R. van & Metzler-Nolte, N. (2004). *Chem. Rev.* **104**, 5931–5985.
- Stepnicka, P., Zabransky, M., Lamac, M., Cisarova, I. & Nemeč, P. (2008). *J. Organomet. Chem.* **693**, 1779–1786.
- Tan, W., Yu, Z., He, W., Wang, L., Sun, J. & Chen, J. (2008). *Organometallics*, **27**, 4833–4836.
- Togni, A. & Hayashi, T. (1995). *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Material Science*. Weinheim: VCH.