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Crystal structure, ^{1}H and ^{13}C NMR spectral studies of 1,2,4,5-oxadiazaborole derivatives

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ABSTRACT

Substituent effects on ^{1}H and ^{13}C NMR chemical shifts of 5-substituted phenyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaboroles (1a-r) were studied respectively. Single and duel substituent parameters were used for the correlation analysis of substituent-induced chemical shifts with σ, F and R constants. The calculations have shown the polar and resonance substituent effects on N-H proton and C=N carbon atoms. The ρ value was found positive for compounds (1a-r), which means that the substituent effect is normal. Additionally, crystal structure of compound (1i) was also studied. Density functional theory (DFT) calculations were carried out to calculate the theoretical chemical shifts, bond distances and bond angles.

1. Introduction

In medicinal chemistry, boron compounds have great potential in drug discovery. These compounds have been reported in the literature as having potential biological activities [1-5]. Some of these are: heterocyclic aminoboron compounds (antituberculosis agents) [6], boron-containing GSK2251052 (antimicrobial agent) [7], oxaboroles (antibacterial prototypes) [8], α-amino cyclic boronates (inhibitors of HCV NS3 protease) [9], benzoxaboroles (anti-inflammatory agents) [10], boronic acid esters (antibacterial agents) [11], boron-containing thiosemicarbazones (antifungal agents) [12], organoboron derivatives (antimicrobial and antifertility activities) [13] and aryl boronate esters (antimicrobial agents) [14]. The other heterocyclic systems containing B-N bonds also show biological activities. Hence, oxadiazaboroles should be interesting compounds for biological activity studies. When we consider the structure of 1,2,4,5-oxadiazaboroles, the presence of oxygen-, nitrogen- and boron- in the five-membered heterocycle system, it can be expected some physiological activities. In relation to this, the study of the transmission of substituent effects on these heteocyclics may provide better insight for their structure-activity relationships.

The chemical shifts in ^{1}H and ^{13}C NMR spectra are often used for the study of the transmission of substituent effects on molecules. Analysis of the substituent chemical shifts (SCS) is based on Hammett or modified Hammett equations [15-18].

In this study, we calculated the ^{1}H and ^{13}C NMR chemical shifts in 5-substituted phenyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaboroles (1a-r) (Figure 1) in order to get an insight into the factors that effect the chemical shifts of the compounds by using linear free energy relationships (LFERs). The equations (1) and (2) have been used for the measurements as given below.

$$\mathrm{SCS} = \rho\sigma + q \qquad (1)$$

$$\mathrm{SCS} = \rho_F\sigma_F + \rho_R\sigma_R + q \qquad (2)$$

In the equations, σ is Hammett substituent constant [18], ρ shows the sensitivity of ^{1}H and ^{13}C NMR chemical shifts to substituent effects, ρ_F and ρ_R give the information about nonconjugative and conjugative effects respectively and q is the intercept. ρ_F and ρ_R are relative measures of the transmission of inductive and resonance effects through the system. When a fit correlation with equation (1) is obtained, the use of equation (2) shows the nonconjugative (ρ_F) and conjugative effects (ρ_R).

Additionally, crystal structure of compound (1i) was also studied.

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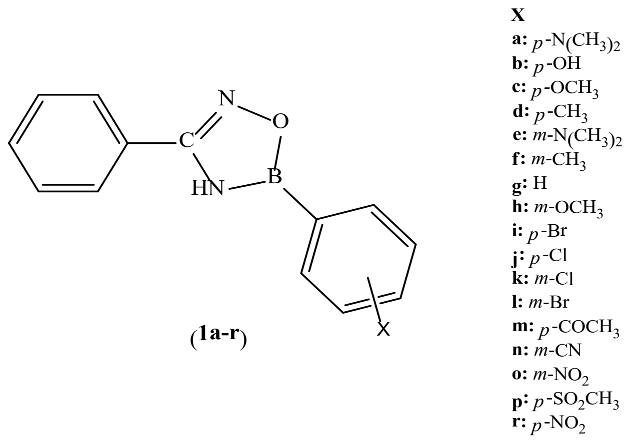


Figure 1. Structure of 5-substituted phenyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaboroles (1a-r).

Computer aid is ranging from molecular design to architectural design [19,20] and also helps to control the experimental data. Therefore, we performed density functional theory (DFT) calculations on compounds (1a-r) to characterize their three-dimensional structures, predict their ^{13}C=N and ^{1}H-N chemical shifts.

2. Materials and methods

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury Plus (300 MHz for proton, 75 MHz for carbon) High Performance Digital FT-NMR spectrometer using DMSO-d_6 for compounds (1a-r) with Me_4Si as the internal standard. The measurements were carried out with low sample concentration (0.1 M) to reduce intermolecular effects. For the synthesis of compounds (1a-r), literature method [21] was applied and the spectral data of the compounds have been reported. All the statistical calculations were done by SigmaPlot program package.

2.1. Calculation method for NMR studies

The calculations for the geometry optimizations of the compounds (1a-r) were done by DFT method on the basis of B3LYP exchange-correlation functional with 6-31++G(d,p) basis set. The ^{1}H and ^{13}C chemical shifts were calculated by the gauge-including atomic orbital (GIAO) method [22-25] at the DFT B3LYP/6-31++G(d,p) level of theory and were referenced to the calculated chemical shifts of DMSO-d_6, optimized at the same level of theory. Gaussian 03W program [26] was used for the calculations and the calculations were also carried out with unrestricted opened-shell formalism.

3. Results and discussion

3.1. X-Ray diffraction analysis

Compound (1i) was crystallized from acetone-hexane mixture, yielding single crystals for X-ray diffraction analysis. Suitable crystal of 1i was selected for data collection which was performed on a Bruker D8 QUEST diffractometer equipped with a graphite-monochromatic Mo-K$_\alpha$ radiation at 296 K. The structure was solved by direct methods using SHELXS-97 [27] and refined by full-matrix least-squares methods on F^2 using SHELXL-97 [27] from within the WINGX [28] suite of software. Hydrogen atoms bonded to C and N were refined using a riding model, with C-H=0.93 Å and N-H=0.86 Å. Molecular diagrams were created using MERCURY [29]. Supramolecular analyses were made and the diagrams were prepared with the aid of PLATON [30]. Details of data collection and crystal structure determinations and selected atomic parameters are given in Tables 1 and 2.

Table 1. Crystal data and structure refinement parameters for 5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (1i).

Empirical formula	$C_{13}H_{10}BBrN_2O$
Formula weight	300.95
Crystal system	Triclinic
Space group	P-1
a (Å)	5.597 (4)
b (Å)	7.624 (4)
c (Å)	15.296 (9)
α (°)	75.92 (2)
β (°)	84.21 (3)
γ (°)	89.64 (3)
V (Å^3)	629.8 (7)
Z	2
D_c (g cm^{-3})	1.587
μ (mm^{-1})	3.25
θ range (°)	3.4-28.6
Measured refls.	11406
Independent refls.	2342
R_{int}	0.063
S	1.18
R1/wR2	0.096/0.281
$\Delta\rho_{max}/\Delta\rho_{min}$ (eÅ^{-3})	0.88/-0.80

The molecular structure of 1i with the atom labeling is shown in Figure 2. The centralring make dihedral angles of 29.15(35)° and 25.92(39)° with the two phenyl rings. The dihedral angle of the phenyl rings is 54.25(28)°. Molecules of 1i are linked into sheets by the combination of N-H···N hydrogen bonds, C-H···π and π···π interactions (Tables 3 and 4). Atom N1 atom acts as hydrogen-bond donor, via atom H1, to atom N2 in the molecule at (x+1, y, z), forming a C(4) chain running which is parallel to the *a* axis (Figure 3). Compound (1i) also contains four C-H···π and one π···π interactions. An intermolecular π···π contact occurs between the two symmetry-related rings of neighbouring molecules. The distance between the ring centroids is 3.563(5) Å. The combination of C-H···π and π···π interactions produce 3D supramolecular network.

3.2. Substituent effects on ^{13}C=N and ^{1}H-N chemical shifts of (1a-r)

We have also obtained experimental and theoretical ^{13}C and ^{1}H NMR chemical shifts of C=N carbon and N-H proton in 5-substituted phenyl-3-phenyl-4,5-

Table 2. Selected bond distances (Å) and angles (º) for 5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (1i).

Bond distances (Å)	**Experimental (X-ray)**	**Calculated (DFT)**
C8-B1	1.587(15)	1.521
B1-N1	1.388(14)	1.443
C7-N1	1.392(13)	1.359
C9-C10	1.404(15)	1.384
B1-O1	1.411(15)	1.411
C7-N2	1.300(14)	1.355
C11-Br1	1.906(10)	1.869
N2-O1	1.480(11)	1.358
Bond angles (º)	**Experimental (X-ray)**	**Calculated (DFT)**
N2-C7-N1	116.8(10)	111.3
N1-B1-O1	106.8(9)	103.7
B1-N1-C7	105.3(9)	107.1
N2-C7-C1	118.0(9)	120.4
N1-B1-C8	132.2(10)	133.1
C7-N2-O1	102.1(8)	106.9
N1-C7-C1	125.2(9)	128.2
O1-B1-C8	120.8(9)	123.0
B1-O1-N2	108.9(8)	110.8
Dihedral angles (º)	**Experimental (X-ray)**	**Calculated (DFT)**
C9-C8-B1-N1	−23.0(2)	0.0
C2-C1-C7-N1	−29.4(15)	0.0

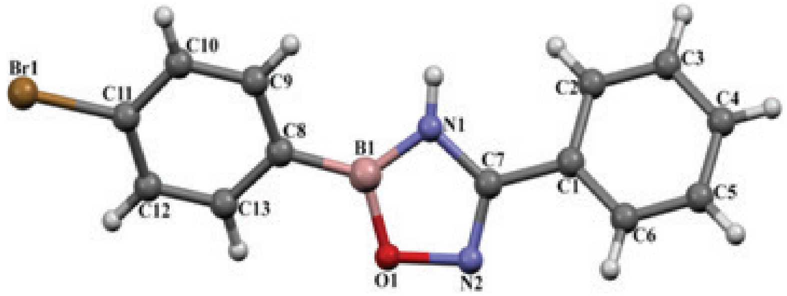


Figure 2. The molecular structure of 1i showing the atom numbering scheme.

Table 3. Hydrogen-bond parameters for 1i (Å, º).

D-H· · ·A	**D-H**	**H···A**	**D···A**	**D-H···A**
N1—H1···N2^{i}	0.86	2.56	3.421 (13)	177
C3—H3···Cg(3)^{ii}	0.93	2.86	3.523 (13)	130
C6—H6···Cg(3)^{iii}	0.93	2.89	3.544 (13)	128
C10—H10···Cg(2)^{iv}	0.93	2.86	3.540 (13)	131
C13—H13···Cg(2)^{v}	0.93	2.87	3.555 (13)	131

Symmetry code: (i) x+1, y, z; (ii) 2-x, -y, 1-z; (iii) 1-x, 1-y, 1-z; (iv) 2-x, 1-y, 1-z; (v) 1-x, -y, 1-z; Cg(2)=C1-C6; Cg(3)=C18-C13

Table 4. π···π interaction distances for 1i (Å).

Cg(I)	**Cg(J)**	**Cg-Cg**	**Perpendicular distance**
Cg(1)	Cg(1)^{i}	3.723(8)	3.563(5)

Symmetry code: (i) 1-x, -y, 1-z; Cg(1)=O1/N2/C7/N1/B1

dihydro-1,2,4,5-oxadiazaboroles (1a-r) (Figure 1) to search the factors that effect the change of the chemical shifts. The correlations between the expimental and theoretical values gave fair results (Table 5); *r*: 0.812 (for ^{13}C chemical shifts) and *r*: 0.670 (for ^{1}H chemical shifts). The values of ^{13}C=N and ^{1}H-N refer to the center peak of DMSO-d_6 which have the values of 39.50 ppm and 2.50 ppm for ^{13}C and ^{1}H respectively. The aromatic ^{1}H NMR and ^{13}C NMR chemical shifts, measured for oxadiazaborole compounds (1a-r) [21] are given in Table 6.

Correlations of ^{13}C and ^{1}H NMR chemical shifts of C=N carbon and N-H proton with σ were done. The good fits with positive ρ values were obtained (Table 7). This shows that the changes in the electron density at C=N carbons and N-H protons are normal and not reverse [31-35]. This means that the substituent dipoles can not polarize π-units (as localized systems) through the space, because of the long distance.

In order to determine the relative importance of substituent resonance and field effects, DSP (dual sub-

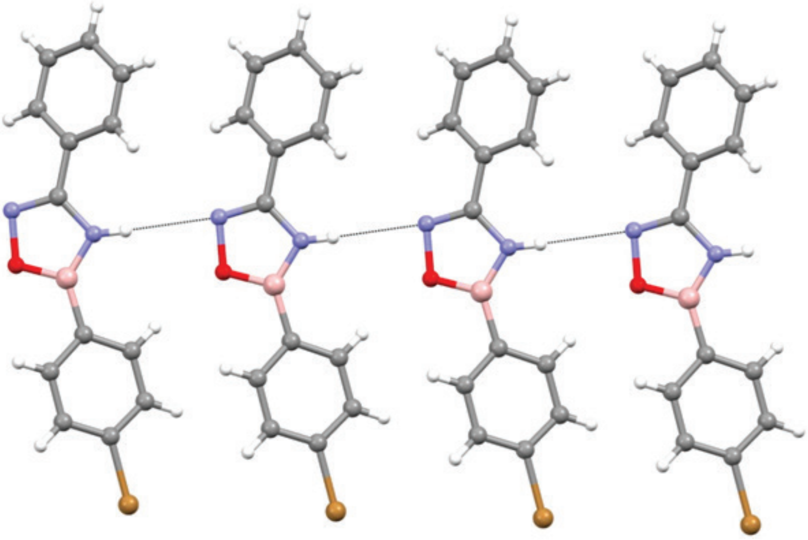


Figure 3. Crystal structure of 1i, showing the formation of a chain along *a* axis generated by N-H···N hydrogen bonds.

Table 5. ^{1}H-N and ^{13}C=N NMR chemical shifts (in ppm) of 5-substituted phenyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaboroles (1a-r) (experimental/**theoretical**).

Compounds	**X**	**γ C=N (ppm)**	**γ N-H (ppm)**
1a	*p*-$N(CH_3)_2$	158.974 **151.127**	9.231 **7.871**
1b	*p*-OH	159.115 **155.339**	9.285 **8.108**
1c	*p*-OCH_3	159.149 **154.938**	9.397 **8.089**
1d	*p*-CH_3	159.206 **156.028**	9.467 **8.197**
1e	*m*-$N(CH_3)_2$	159.231 **148.350**	9.447 **7.381**
1f	*m*-CH_3	159.259 **156.952**	9.489 **8.178**
1g	H	159.267 **156.762**	9.533 **8.235**
1h	*m*-OCH_3	159.038 **153.781**	9.533 **7.853**
1i	*p*-Br	159.294 **155.437**	9.626 **8.171**
1j	*p*-Cl	159.294 **155.990**	9.607 **8.148**
1k	*m*-Cl	159.294 **156.930**	9.618 **8.112**
1l	*m*-Br	159.278 **155.488**	9.701 **8.097**
1m	*p*-$COCH_3$	159.420 **156.809**	9.711 **8.299**
1n	*m*-CN	159.328 **157.372**	9.686 **8.128**
1o	*m*-NO_2	159.404 **156.925**	9.809 **8.177**
1p	*p*-SO_2CH_3	159.507 **156.711**	9.778 **8.282**
1r	*p*-NO_2	159.493 **156.972**	9.831 **8.250**
r		**0.812**[a]	**0.670**[b]

a) Except *m*-$N(CH_3)_2$ (1e); b) Except *m*-$N(CH_3)_2$ (1e) and *m*-OCH_3 (1h); *r*, Correlation coefficient

stituent parameter) analyses of the ^{13}C=N and ^{1}H-N chemical shifts were carried out. The ρ_F and ρ_R values are given in Table 8 (F and R substituent constants are taken from [18]). As given in Table 8, ρ_R values are greater than the corresponding ρ_F values. This shows that C=N carbon and N-H proton in the heterocyclic ring are more sensitive towards the substituent resonance effects through resonance Structures III, IV and V (Figure 5) rather than polar substituent effects (Figure 4, Structures I and II).

Table 6. Aromatic ^{1}H and aromatic ^{13}C NMR chemical shifts (in ppm) of 5-substituted phenyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaboroles (1a-r) (experimental).

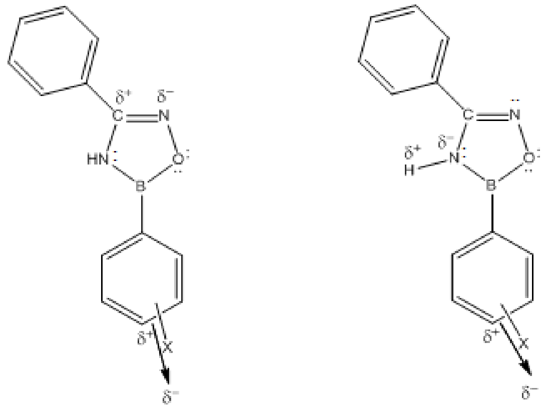
Compounds (Substituent, X)	$\gamma_{\text{Aromatic, H}}$ (ppm)	$\gamma_{\text{Aromatic, C}}$ (ppm)
1a (*p*-N(CH_3)$_2$)	7.095-7.063, 6.882, 6.678-6.651, 5.917	152.098, 135.169, 130.564, 128.896, 126.994, 126.212, 111.474
1b (*p*-OH)	7.040-7.007, 6.853-6.825, 6.633-6.610, 5.975-5.946	160.177, 135.829, 130.713, 128.991, 126.895, 126.269, 118.007, 115.403
1c (*p*-OCH_3)	7.084-6.973, 6.680-6.649, 6.183	161.627, 135.660, 130.689, 128.937, 126.806, 126.241, 113.932
1d (*p*-CH_3)	7.078-7.047, 6.937, 6.662-6.641, 6.414	140.842, 133.965, 130.747, 128.979, 128.944, 126.764, 126.279
1e (*m*-N(CH_3)$_2$)	7.083-7.030, 6.678-6.656, 6.483-6.334, 6.007-5.971	150.145, 130.787, 128.997, 128.894, 126.801, 126.316, 125.404, 121.716, 117.611, 115.179
1f (*m*-CH_3)	7.079-7.032, 6.834-6.789, 6.648-6.616, 6.477-6.417	137.221, 134.509, 131.788, 131.028, 130.784, 129.005, 128.218, 128.115, 126.752, 126.299
1g (H)	7.085-7.021, 6.662-6.565	133.893, 131.111, 130.762, 128.967, 128.249, 126.707, 126.291
1h (*m*-OCH_3)	7.082-7.050, 6.674-6.495	159.037, 130.573, 129.371, 128.760, 126.440, 126.049, 125.835, 118.534, 116.672
1i (*p*-Br)	7.099-7.067, 7.006-6.979, 6.872-6.838, 6.708-6.681	135.809, 131.339, 130.815, 128.979, 126.543, 126.241, 125.192
1j (*p*-Cl)	7.066-7.040, 6.690-6.675	136.169, 135.642, 130.793, 128.964, 128.406, 126.570, 126.249
1k (*m*-Cl)	7.069-7.038, 6.973, 6.684-6.626	133.374, 132.176, 130.909, 130.825, 130.371, 128.977, 126.495, 126.209
1l (*m*-Br)	7.426-6.639	139.261, 133.801, 132.522, 130.846, 130.685, 128.994, 126.489, 126.207, 122.148
1m (*p*-$COCH_3$)	7.179, 7.100-7.068, 6.698-6.676	138.520, 134.129, 130.888, 129.024, 128.091, 127.765, 126.539, 126.314
1n (*m*-CN)	7.433, 7.336, 7.137-7.050, 6.865-6.813, 6.710-6.688	138.093, 137.357, 134.409, 130.927, 129.465, 129.052, 128.071, 126.407, 126.208, 118.667
1o (*m*-NO_2)	7.863, 7.487-7.390, 7.080-7.048, 6.924-6.871, 6.695-6.674	147.691, 139.997, 130.922, 129.975, 129.021, 128.181, 128.089, 126.409, 126.228, 125.684
1p (*p*-SO_2CH_3)	7.294, 7.185, 7.084-7.052, 6.687-6.665	142.888, 134.770, 134.671, 130.983, 129.082, 128.119, 126.579, 126.455, 126.325, 125.665
1r (*p*-NO_2)	7.461, 7.298, 7.091-7.060, 6.692-6.677	149.123, 135.099, 130.930, 129.013, 126.387, 126.284, 122.954

Table 7. Statistical results of SSP (single substituent parameter) correlation analysis of ^{13}C=N and ^{1}H-N NMR chemical shifts of (1a-r) against *σ*.

Bonds	*r*	*ρ*	*q*	*n*
^{13}C=N	0.880	0.289	159.22	17
^{1}H-N	0.983	0.388	9.51	17

Table 8. Statistical results of DSP (dual substituent parameter) correlation analysis of ^{13}C=N and ^{1}H-N NMR chemical shifts of (1a-r) against F and R constants.

Bonds	*r*	ρ_F	ρ_R	*q*	ρ_F/ρ_R	*n*
^{13}C=N	0.997	0.273	0.354	159.27	0.771	10
^{1}H-N	0.987	0.388	0.412	9.53	0.942	10



Structure I Structure II

Figure 4. The polar substituent effect in compounds (1a-r).

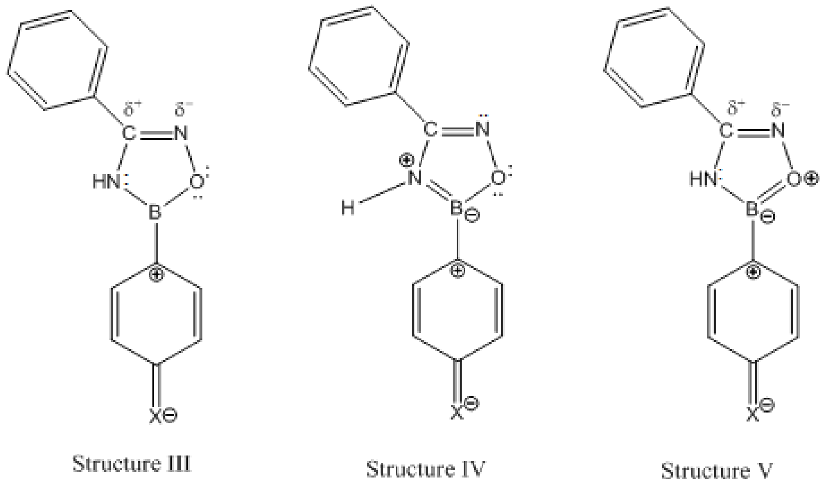


Figure 5. The resonance Structure III, IV and V of compounds (1a-r).

4. Conclusions

In this study, we have carried out the combined experimental and theoretical spectroscopic analysis of 5-substituted phenyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaboroles (1a-r), using ^{1}H, ^{13}C NMR techniques and DFT. In general, good correlations between experimental and calculated values have been observed. X-ray studies helped in establishing the structure with optimized geometric parameters (bond lengths, bond angles and dihedral angles) which are determined by DFT theory and compared with the experimental data. The substituent chemical shift (SCS) values with applied linear free energy relationships (LFERs) analysis were correlated with Hammett type substituent constants and substituent effects from the aryl groups were observed to be efficiently transmitted to the heterocyclic framework of the compounds. The $\boldsymbol{\rho}_F/\rho_R$ values indicated that the resonance effect is significant at the C=N carbon and N-H proton of compounds (1a-r).

Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1454233. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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