# Conformation of *N*-Cyclopropylcarbonylureas. Solvent Polarity Dependent Chemical Shifts

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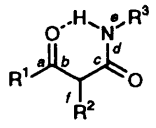
The relation between solvent polarity and the chemical shifts of two diastereoisomeric *N*-cyclopropylcarbonylureas **1** and **2** was examined to elucidate their conformations in solution. In non-polar solvents, where intramolecular hydrogen bonding was playing an important role, their conformations were estimated to be similar to that of **1** in its crystalline state.

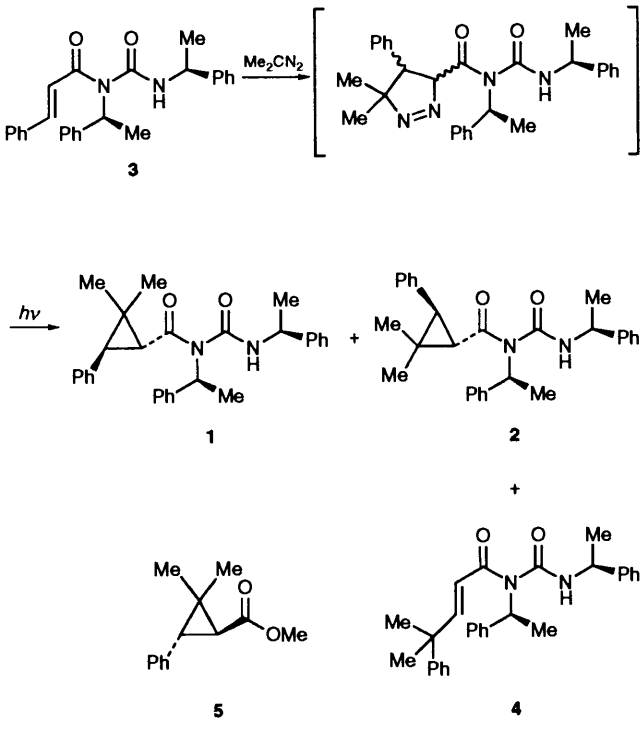
Recently we have been developing the synthetic utility of chiral acylureas[1] which possess unique structural features—three sequential amide units and intramolecular hydrogen bonding among them. Owing to this, the conformation of acylureas should be regulated. Our particular interest is to estimate the conformation of chiral acylureas in solution in order to design and improve stereoselective syntheses using them. Similar to diamides, the conformation-directing effects of a single intramolecular amide–amide hydrogen bond[2] are important in acylureas. Conformationally, acylurea of type **A** has rotational freedom around six σ-bonds (*a–f*). Three of them, amide bonds



**A**

*b*, *c* and *d*, have a partial π-bond character[3] which regulates the conformation of **A** to a certain extent, although an additional control is required to fix their conformations to a single one. In this paper, we describe the relationship between the conformation of acylureas and the strength of intramolecular hydrogen bonding.

Introduction of strong intramolecular hydrogen bonding between the carbonyl oxygen and N–H hydrogen makes the resulting six-membered ring very rigid (bonds *b*, *c* and *d* lose rotational freedom completely). Rotations about bonds *e* and *f* are restricted by the steric repulsion between the carbonyl group and the substituents $R^2$ and $R^3$. The remaining rotation about bond *a* could be controlled by a proper choice of substituent $R^1$ which sterically interacts with $R^2$. In order to satisfy the above mentioned prerequisites for conformational control, we have designed an acylurea possessing the cyclopropyl substituent ($R^1$) since substituted cyclopropanes are known as a conformational constraint.[4] The rigidity of the cyclopropane ring may contribute to the steric interaction between $R^1$ and $R^2$. The model compounds, *N*-cyclopropylcarbonylureas **1** and **2**, were synthesized by the following reaction. The 1,3-dipolar cycloaddition of 2-diazopropane[5] to acylurea **3** generated an unstable 3*H*-pyrazole intermediate which was subsequently photolysed with UV irradiation to give **1** (30%) and **2** (52%) together with acylurea **4** (8%). The crystal structure of **1** was unequivocally determined by a single crystal X-ray diffraction analysis as shown in Fig. 1. In order to minimize the steric repulsion between carbonyl [C=O(2)] and the neighbouring two phenylethyl groups, the smallest groups, H(6) and H(7), are directed towards this carbonyl. As a result,



the C(7) substituted methyl and phenyl groups face towards the cyclopropane moiety. In order to avoid the steric repulsion between the bulkier cyclopropane substituents and the C(7) substituents, the proton H(5) takes the position in the middle of the C(7) substituted methyl and phenyl groups, which also regulates the geometrical relation between the cyclopropane moiety and the carbonyl [C=O(1)] to the energetically best location. The carbonyl group takes the position between H(3) and the methyl C(11) group. Table 1 shows the main geometrical interactions responsible for this conformation.

Since the phenyl group substituted at the cyclopropane ring faces towards the phenyl of the neighbouring phenylethyl group, the *ortho*-proton substituted at the former phenyl group ($H_a$) should be shielded by the latter phenyl group in $^1H$ NMR spectroscopy if this conformation is kept in solution. Therefore, the chemical shift of $H_a$ can be used as a unique index to account for the conformation of **1** in solution. The rigidity of its conformation should be related to the strength of the intramolecular hydrogen bonding. Fig. 2 shows the plots of the chemical shift of $H_a$ against the sum of $[E_T(30) + 100\beta_{KT}]$

**Table 1** Main geometrical interactions responsible for the observed conformation

| Atomic distance/Å | | | | Angle/° | |
|---|---|---|---|---|---|
| N(2)···O(1) | 2.545(4) | H(2)···O(1) | 1.84(4) | N(2)–H(2)···O(1) | 133(3) |
| C(3)···O(1) | 2.809(4) | H(3)···O(1) | 2.43(3) | C(3)–H(3)···O(3) | 104(2) |
| C(6)···O(2) | 2.804(4) | H(6)···O(2) | 2.42(4) | C(6)–H(6)···O(2) | 99(2) |
| C(7)···O(2) | 2.678(4) | H(7)···O(2) | 2.11(4) | C(7)–H(7)···O(2) | 113(2) |

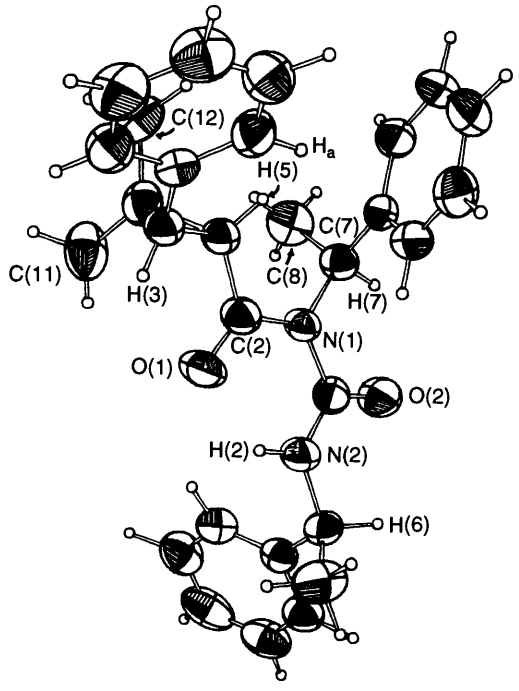



**Fig. 1** ORTEP view of **1**

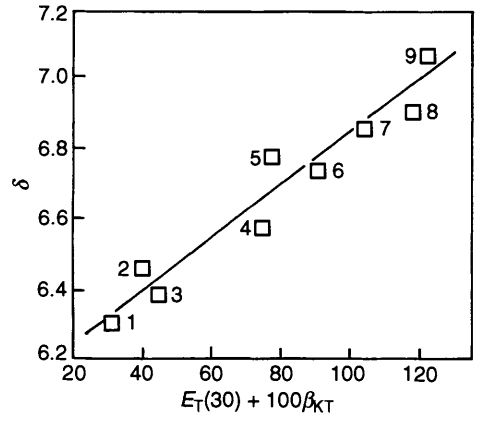



**Fig. 2** Chemical shift of $H_a$ **1** *vs.* $E_T(30) + 100\beta_{KT}$: solvent 1, [$^2H_{12}$]cyclohexane; 2, $CDCl_3$; 3, [$^2H_6$]benzene; 4, [$^2H_8$]1,4-dioxane; 5, $CD_3CN$; 6, [$^2H_6$]acetone; 7, [$^2H_5$]pyridine; 8, [$^2H_6$]$Me_2SO$; 9, $CD_3OD$

which was reported recently as a good solvent parameter to be used for the study of intramolecular hydrogen bonding.[6] A better linear relationship was observed with this parameter ($r$ = 0.97) than with the empirical solvent parameter $E_T(30)$[7] ($r$ = 0.80) or the (Kamlet–Taft) solvent hydrogen bond basicity $\beta_{KT}$[8] ($r$ = 0.94). From this figure, clearly non-polar solvents strengthen the intramolecular hydrogen bonding that results in the large upfield shift of $H_a$. The conformation of **1** in non-polar solvents is quite similar to the one found in its crystal structure. The NOE relationship (in $C_6D_6$) between H(5) and the methyl

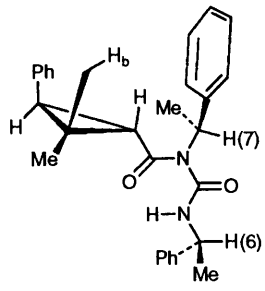



**Fig. 3** Estimated conformation of **2** in non-polar solvents

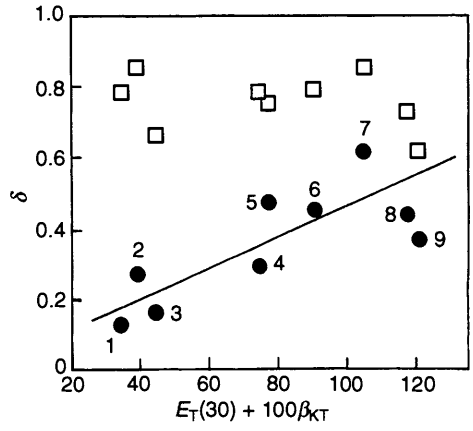



**Fig. 4** Chemical shifts of $H_b$ (**2**, –●–) and methyl protons C(12)$H_3$ (**1**, □) *vs.* $E_T(30) + 100\beta_{KT}$. Solvent numbers are in Fig. 2.

group C(8) also supported this conformation. According to the increase of the solvent polarity, the chemical shift of $H_a$ gradually shifted to lower field due to the looseness of the intramolecular hydrogen bonding which allowed the rotation about the C(2)–N(1) bond to release the steric repulsion between the facing phenylethyl and cyclopropane moieties.

Unfortunately, the cyclopropane **2** is an oily compound. However, by a similar consideration of its steric interactions as for**1**, it might adopt the conformation depicted in Fig. 3 in non-polar solvents. Since **2** is diastereoisomeric to **1**, the methyl group substituted at the cyclopropane ring is exposed to the shielding zone of the phenyl of the phenylethyl group. Fig. 4 shows the relation between the chemical shift of the methyl group ($H_a$) and [$E_T(30) + 100\beta_{KT}$]. A strong shielding effect was observed for this methyl in non-polar solvents. Similarly to **1**, its gradual lower field shift was observed according to the increase of solvent polarity, though the linearity was poor. These observations verify the estimated conformation of **2** in non-polar solvents. In contrast, the chemical shift of the methyl group C(12) of **1** appears around $\delta$ 0.8–0.7 and is almost independent of the solvent polarity as shown in Fig. 4. It is appropriate to make an assumption that the shift value of $H_b$ becomes almost equivalent to this value without the intramolecular hydrogen bonding. Since the *N*-carbamoylamide moiety is located on the plane of symmetry of the cyclopropane ring, the anisotropy caused by it affects almost equally the substituents at the cyclopropane ring in both diastereoisomers

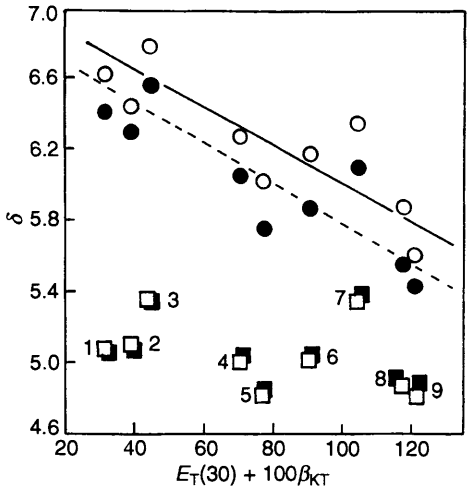



**Fig. 5** Chemical shifts of H(6) for **1** (□) and **2** (■) and H(7) for **1** (—○—) and **2** (- -●- -) *vs.* $E_T(30) + 100\beta_{KT}$. Solvent numbers are in Fig. 2.

in the absence of intramolecular hydrogen bonding. Under the circumstances, the chemical shift of $H_b$ should be similar to that of the corresponding methyl protons ($\delta$ 0.92 in $CDCl_3$) of **5** prepared from the methanolysis of **1**. The above mentioned estimated shift value for $H_b$ without hydrogen bonding is similar to this value.

In both diastereoisomers, the proton H(7) is located in the deshielding zone of the carbonyl group [C=O(2)] (due to the restricted geometry of the phenylethyl group which faces towards the cyclopropane ring) by intramolecular hydrogen bonding. Release of this restriction by solvation should cause the upfield shift of H(7). Fig. 5 shows this tendency. In this case the plot of its chemical shift against the parameter [$E_T(30) + 100\beta_{KT}$] also gave a relatively better relation than against $E_T$ or $\beta_{KT}$. In contrast to this solvent polarity dependent chemical shift of H(7), the chemical shift of H(6) is almost independent of solvent polarity.

As we have demonstrated, the cyclopropane moiety is a good conformational constraint and the intramolecular hydrogen bonding plays an important role for fixation of the conformation of *N*-cyclopropylcarbonylureas in solution.

## Experimental

*General Details.*—M.p.s were determined on a Yanako MP-S3 melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO A-202 spectrometer. NMR spectra were recorded on JOEL JNM FX270 and GSX500 spectrometers. For the solvent effect study, the $^1H$ NMR spectrum of **1** ($2.2 \times 10^{-2}$ mol $dm^{-3}$) was recorded at 19 ± 2 °C on a Varian XL400 instrument. Coupling constants ($J$) are given in Hz. Mass spectra were obtained on a Hitachi RMU-7M mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 analyser. Reaction solutions were concentrated on a rotary evaporator at 15–20 mmHg. Chromatographic separations were accomplished by flash column chromatography on silica gel (Fuji gel BW 200). Separation of diastereoisomers was carried out by a preparative HPLC run; column Merck LiChrosorb Si60 (7 μm, 10 × 250 mm), hexane–ethyl acetate as eluent.

N-[(S)-1-*Phenylethyl*]-N-[(S)-1-*phenylethylcarbamoyl*]-3-*phenylacrylamide* **3**. This was prepared according to the reported method.[1] **3**: colourless crystals; m.p. 98.5–99.5 °C (hexane–ethyl acetate) (Found: C, 78.47; H, 6.57; N, 7.06. $C_{26}H_{26}N_2O_2$ requires C, 78.36; H, 6.58; N, 7.03); $[\alpha]_D^{22}$ +193.9 (*c* 1.00, $CHCl_3$); $\nu_{max}$(KBr)/$cm^{-1}$ 3350 (NH), 1700 (C=O) and 1650 (C=O); $\delta_H$(270 MHz; $CDCl_3$) 1.52 (3 H, d, *J* 7.0), 1.76 (3 H, d, *J* 7.0), 5.08 (1 H, qd, *J* 7.0 and 7.0), 6.28 (1 H, q, *J* 7.0), 6.59 (1 H, d, *J* 15.4), 7.42–7.17 (m, 15 H), 7.60 (1 H, d, *J* 15.4) and 8.95 (1 H, s); $\delta_C$(125 MHz; $CDCl_3$) 18.40 (q), 22.58 (q), 50.78 (d), 51.43 (d), 120.32 (d), 125.99 (d), 127.15 (d), 127.21 (d), 127.99 (d), 128.64 (d), 128.76 (d), 130.14 (d), 134.52 (s), 141.86 (s), 143.26 (s), 143.98 (d), 154.60 (s) and 169.37 (s) [$MH^+$ (FAB), 399.2073. $C_{26}H_{27}N_2O_2$ ($MH^+$), requires 399.2072].

*Cyclopropanation of Acrylylurea* **3**.—To a stirring solution of **3** (299.8 mg, 0.753 mmol) in diethyl ether (15 $cm^3$) was added a tetrahydrofuran (THF) solution of dimethyldiazomethane at room temp. until the pinkish colour of dimethyldiazomethane disappeared. The resulting mixture was irradiated by high pressure mercury lamp (USHIO, 450 W) under bubbling of argon gas for 8 h. After evaporation of solvent, the residue was chromatographed on silica gel and further purified by HPLC to give **1** (100.8 mg, 30%), **2** (171.0 mg, 52%) and **4** (27.4 mg, 8%).

(1R,3R)-N-[(S)-1-*Phenylethyl*]-N-[(S)-1-*phenylethylcarbamoyl*]-2,2-*dimethyl*-3-*phenylcyclopropanecarboxamide* **1**. Colourless crystals; m.p. 142.5–144.0 °C (hexane–ethyl acetate) (Found: C, 78.80; H, 7.12; N, 6.71. $C_{29}H_{32}N_2O_2$ requires C, 79.06; H, 7.32; N, 6.36%); $[\alpha]_D^{22}$ +80.0 (*c* 0.90, $CHCl_3$); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3725 (NH), 1695 (C=O) and 1638 (C=O); $\delta_H$(270 MHz; $CDCl_3$) 0.84 (3 H, s), 1.54 (3 H, d, *J* 7.0), 1.80 (3 H, d, *J* 7.0), 1.99 (1 H, d, *J* 5.5), 2.78 (1 H, d, *J* 5.5), 5.08 (1 H, dq, *J* 7.0 and 7.0), 6.43 (2 H, m) and 7.01–7.44 (15 H, m); $\delta_C$(125 MHz; $CDCl_3$) 18.13 (q), 20.03 (q), 21.70 (q), 22.97 (q), 31.56 (s), 34.72 (d), 36.86 (d), 50.77 (d), 50.80 (d), 125.80 (d), 126.03 (d), 126.15 (d), 126.78 (d), 127.09 (d), 127.92 (d), 128.30 (d), 128.44 (d), 128.61 (d), 129.02 (d), 137.10 (s), 142.74 (s), 143.82 (s), 154.94 (s) and 175.74 (s); *m/z* 440 ($M^+$, 10%), 308 (7), 204 (24), 145 (84), 120 (27), 105 (100), 91 (30) and 77 (43).

(1S,3S)-N-[(S)-1-*Phenylethyl*]-N-[(S)-1-*phenylethylcarbamoyl*]-2,2-*dimethyl*-3-*phenylcyclopropanecarboxamide* **2**. Colourless oil; $[\alpha]_D^{22}$ +31.3 (*c* 1.48 $CHCl_3$); $\nu_{max}$(NaCl)/$cm^{-1}$ 3270 (NH), 1695 (C=O) and 1638 (C=O); $\delta_H$(270 MHz; $CDCl_3$) 0.26 (3 H, s), 1.14 (3 H, s), 1.54 (3 H, d, *J* 7.1), 1.88 (3 H, d, *J* 7.1), 1.96 (1 H, d, *J* 5.7), 2.83 (1 H, d, *J* 5.8), 5.06 (1 H, dq, *J* 7.1 and 7.1), 6.27 (1 H, q, *J* 7.1), 7.37–7.00 (15 H, m) and 9.43–9.31 (1 H, br s); $\delta_C$(125 MHz; $CDCl_3$) 18.76 (q), 19.79 (q), 20.93 (q), 22.78 (q), 31.56 (s), 35.34 (d), 33.73 (d), 50.62 (d), 51.78 (d), 125.55 (d), 125.91 (d), 126.25 (d), 126.71 (d), 127.04 (d), 128.08 (d), 128.52 (d), 128.56 (d), 128.74 (d), 137.44 (s), 142.24 (s), 143.61 (s), 154.55 (s) and 175.29 (s); *m/z* 440 ($M^+$, 6%), 308 (5), 204 (12), 145 (61), 132 (23), 105 (100), 91 (19) and 77 (29) [$MH^+$ (FAB), 441.2540. $C_{29}H_{33}N_2O_2$ ($MH^+$), requires 441.2542].

N-[(S)-1-*Phenylethyl*]-N-[(S)-1-*phenylethylcarbamoyl*]-3-*methyl*-3-*phenylbut*-1-*enecarboxamide* **4**. White crystals; m.p. 89.5–91.0 °C; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3725 (NH), 1695 (C=O) and 1618 (C=O); $\delta_H$(270 MHz; $CDCl_3$) 1.23 (3 H, s), 1.26 (3 H, s), 1.52 (3 H, d, *J* 7.1), 1.69 (3 H, d, *J* 7.2), 5.05 (1 H, dq, *J* 7.1 and 7.1), 5.86 (1 H, d, *J* 15.4), 6.28 (1 H, d, *J* 7.2), 6.97 (1 H, d, *J* 15.4), 7.38–7.01 (15 H, m) and 9.40–9.28 (1 H, br s); $\delta_C$(125 MHz; $CDCl_3$) 18.37 (q), 22.81 (q), 27.50 (q), 28.01 (q), 41.17 (s), 50.82 (d), 120.68 (d), 126.01 (d), 126.06 (d), 126.35 (d), 126.86 (d), 127.19 (d), 128.33 (d), 128.66 (d), 128.73 (d), 141.99 (s), 143.56 (s), 146.16 (s), 154.89 (s), 156.68 (d) and 170.20 (s); *m/z* 440 ($M^+$, 1%), 308 (7), 293 (19), 217 (13), 174 (45), 158 (15), 145 (20), 120 (61), 105 (100), 91 (23) and 77 (46) [$MH^+$ (FAB), 441.2550. $C_{29}H_{33}N_2O_2$ ($MH^+$), requires 441.2542].

*Methanolysis of* **3**.—To a solution of **3** (50.3 mg, 0.114 mmol) in 0.5 $cm^3$ of methanol was added a methanol solution (4 $cm^3$) of sodium methoxide (10 equiv.). The resulting mixture was refluxed for 20 min and quenched with 1 mol $dm^{-3}$ HCl (4.5 $cm^3$). Methanol was evaporated and the product was extracted with chloroform. After drying over anhydrous $MgSO_4$, the solvent was evaporated and the residue was chromatographed

on silica gel (eluent; hexane–ethyl acetate = 4:1) and then further purified by preparative HPLC to give methyl (1*S*,3*S*)-2,2-dimethyl-3-phenylcyclopropanecarboxylate **5** (14.9 mg, 64%): $[\alpha]_D^{22}$ −36.0 (*c* 0.72 $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); $\delta_H$(270 MHz; $CDCl_3$) 0.92 (3 H, s), 1.38 (3 H, s), 1.96 (1 H, d, *J* 5.9), 2.70 (1 H, d, *J* 5.9), 3.72 (3 H, s) and 7.12–7.33 (5 H, m) [$M^+$ (EI), 204.1157. $C_{13}H_{16}O_2$ ($M^+$) requires 204.1150. $M^+$ − AcO, 145.0996. $C_{11}H_{13}$ ($M^+ - CO_2CH_3$) requires 145.1017].

*X-Ray Crystal Structure Determination of Compound* **1**.—A colourless rod crystal of **1** having approximate dimensions of 0.30 × 0.40 × 0.20 mm, mounted on a glass fibre, was used for the X-ray study.

*Crystal Data*. $C_{29}H_{32}N_2O_2$, $M$ = 440.59, monoclinic, space group $P2_1$, $a$ = 13.192(3), $b$ = 6.589(1), $c$ = 15.512(3) Å, $\beta$ = 113.48(1)°, $V$ = 1236.7(4) Å$^3$, $Z$ = 2, $D_c$ = 1.18 g cm$^{-3}$, $F(000)$ = 472, $\mu$(Mo-K$\alpha$) 0.7 cm$^{-1}$.

*Data collection, structure solution and refinement*. The intensity data were collected on a Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-K$\alpha$ radiation ($\lambda$ 0.709 30 Å) using $\omega$–2$\theta$ scan technique in the range of $2\theta \leq 50°$. Out of 2146 total reflections, 2036 reflections having intensities greater than $3\sigma(I)$ were used in the refinements. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. The structure was solved by direct methods using the SPD/VAX (Enraf-Nonius & B. A. Frenz and Associates). Least-squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at $R$ 0.034 ($R_w$ 0.033).

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. For details of the CCDC deposition scheme see 'Instructions for Authors (1994),' *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1.

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