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PHOSPHONIC SYSTEMS. PART 8. SOLUTION AND SOLID-STATE CONFORMATION OF DIASTEREOMERIC ADDUCTS OF DIETHYL PROP-2-ENYLPHOSPHONATE TO *p*-NITROBENZALDEHYDE

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A mixture of diastereomeric adducts of lithiated diethyl prop-2-enylphosphonate to *p*-nitrobenzaldehyde was separated and the solution and the solid-state structures of the individual stereoisomers were studied. Conformational analysis demonstrated that in solution the most populated rotamer involves in both cases *trans* orientation of the PO_3Et_2 and $O_2NC_6H_4$ groups and a *gauche* relationship of the phosphoryl and hydroxyl groups. In the solid state the crystal structure determination demonstrated that the molecules exist in the same conformation as in solution, although the P=O ··· H—O hydrogen bonding changed from intramolecular to intermolecular (dimeric) interactions.

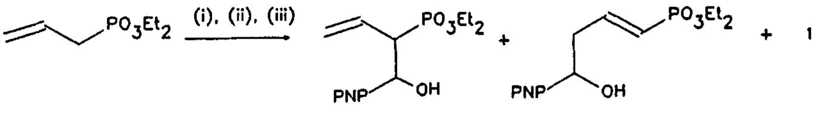
INTRODUCTION

Conjugated dienes can be prepared via the Wittig–Horner reaction using relatively unreactive substrates such as diethyl arylmethanephosphonates or their vinylogues.[1] Although lithiated allylic phosphonates react with aldehydes to yield α-adducts as kinetic products, in the absence of other functional groups stabilising the incipient diene these 2-hydroxyalkylphosphonates cannot always serve as effective precursors for the diene products.[2] On deprotonation, the kinetic α-adducts often isomerize instead to the corresponding γ-derivatives via reversal of the addition step. Since the addition of an allylphosphonate to an aldehyde generates a pair of diastereomeric products, we were interested in the relationship between the relative configurations of the two chiral centres in the α-adduct and the conformation of the compound, and also the reactivity of the individual diastereomers in the diene-forming and in the retro addition steps.

In this work we carried out structural (solution and solid-state) studies of the diastereomeric products of the nucleophilic addition of diethyl prop-2-enylphosphonate (**1**) to *p*-nitrobenzaldehyde. It was known[3] that this reaction yields a crystalline product, hence we hoped that the individual diastereomers could be separated and their structures could be studied independently, in solution and in the solid-state, by means of x-ray diffraction.

RESULTS AND DISCUSSION

The reaction of lithiated **1** with *p*-nitrobenzaldehyde (PNPCHO) at −78 °C results in an equilibrium mixture which, after aqueous work-up, gives the products shown in equation (1).[2]



(1)

1 2 3

20% 49% 31%

(i) BuLi, THF, −78 °C
(ii) PNPCHO, −78 °C to
(iii) aq NH_4Cl, −78 to +20 °C

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The α-adduct **2**, consisting of two diastereomers (**2a** and **2b**) in a *ca* 1:1 ratio, was isolated from the crude product containing the γ-adduct **3** and the unreacted **1** by column chromatography, and separated into pure stereoisomers by means of preparative TLC. The individual diastereomers were examined by NMR spectroscopy (Table 1) and the relative configurations (*threo, erythro*) were assigned using the observed values of the $^3J_{AB}$ (vicinal) coupling constants in the ^1H NMR spectra. The assignment was based on the previously observed[4] attractive interactions between the phosphoryl group and the 2-hydroxy substituent and the preferred *trans* location of the PO_3R_2 and the 2-aryl groups. A similar trend in the J_{AB} values (7 vs 1 Hz) was reported for the two diastereomers of diphenyl(2-hydroxyalkyl)phosphine oxides.[5] For each stereoisomer three stable staggered conformations exist with respect to the rotation about the $C_\alpha-C_\beta$ bond (Figure 1).

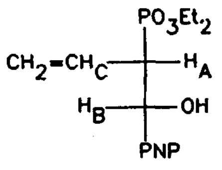
Table 1. Selected data for the diastereomers of diethyl 1-[(hydroxy)(*p*-nitrophenyl)methyl] prop-2-enylphosphonate

Parameter	**2a** (*threo*)	**2b** (*erythro*)
M.p. (°C)	116·2	125·8
NMR ($CDCl_3$):		
δ_P (ppm)	27·3	27·7
δ_H(A) (ppm)	2·78	2·81
δ_H(B) (ppm)	5·12	5·00
δ_H(C) (ppm)	5·82	5·51
$^2J_{AP}$ (Hz)	22·0	18·5
$^3J_{AC}$ (Hz)	10·0	9·5
$^3J_{AB}$ (Hz)	2·2	9·5
$\delta_C(\alpha)$ (ppm)	50·78	51·67
$\delta_C(\beta)$ (ppm)	70·84	72·62
$^1J_{\alpha CP}$ (Hz)	136·1	133·6

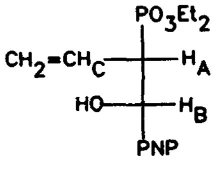
The observed vicinal coupling constants $^3J_{AB}$ (Table 1) are related to the populations (x_1, x_2, x_3) and the calculated vicinal coupling constants of the individual rotamers (^3J_g and ^3J_t) in the following way:

$$^3J_{AB} = x_1\,^3J_g(X_1) + x_2\,^3J_{g'}(X_2) + x_3\,^3J_t(X_3)$$

By applying the approach of Haasnoot *et al.*[6] and using



2a (threo)



2b (erythro)

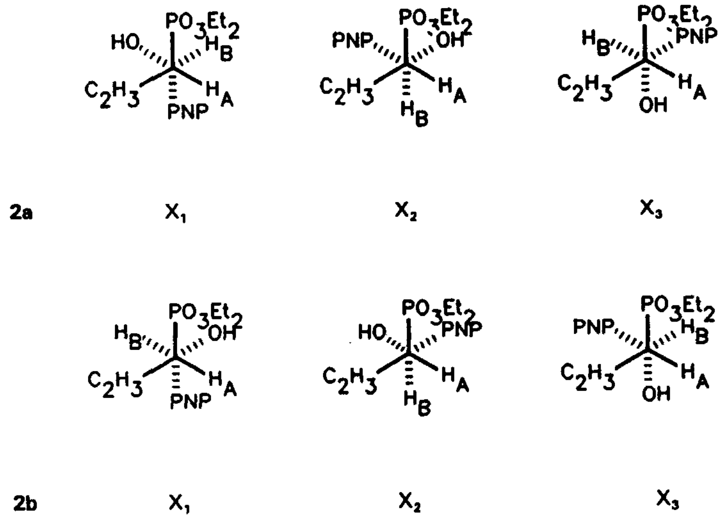


Figure 1. Staggered conformations of *threo*- and *erythro*-diethyl 1-[(hydroxy)(*p*-nitrophenyl)methyl] prop-2-enylphosphonate

the available[7] group electronegativities, the theoretical vicinal proton–proton coupling constants (J_g and J_t) could be calculated. Since the molecules of **2** contain only one pair of vicinal hydrogen atoms at the $C_{\alpha'}$, C_β carbons, we had to simplify the equation by combining for each diastereomer the rotamers involving the *gauche* orientation of the H_A, H_B hydrogens and averaging the calculated ^3J_g value for these two rotamers:

$$^3J_{AB} = (x_1 + x_2)\,^3J_{g(av)} + x_3\,^3J_t(X_3) \qquad \text{for } \mathbf{2a}$$

$$^3J_{AB} = x_1\,^3J_t(X_1) + (x_2 + x_3)\,^3J_{g(av)} \qquad \text{for } \mathbf{2b}$$

where

$$^3J_{g(av)} = 0{\cdot}5[^3J_g(X_1) + {}^3J_{g'}(X_2)] \qquad \text{for } \mathbf{2a}$$

and

$$^3J_{g(av)} = 0{\cdot}5[^3J_g(X_2) + {}^3J_{g'}(X_3)] \qquad \text{for } \mathbf{2b}$$

The results are given in Table 2. Irrespective of the accuracy of the treatment, the conformational preferences are obvious. The major factors determining the distribution of rotamers are the repulsive interactions between the PO_3Et_2 and PNP groups and the attractive interactions between the former group and the 2-hydroxy function. As a consequence, although for **2a** the combined population of the two rotamers (X_1, X_2) was calculated to be quantitative, we believe that the first rotamer (X_1) represents the almost exclusive form of the compound in $CDCl_3$ solution. This conclusion is supported by the results obtained for **2b**, which exists in chloroform solely as rotamer X_1 (the only one which involves *trans* orientation of PO_3Et_2/PNP groups and *gauche* orientation of PO_3Et_2/OH groups). Since the dilution of the solutions of **2** in CCl_4 had no effect on the IR spectra of these compounds, we interpret the attraction between the phosphonate and the 2-hydroxy group as indicative of the intramolecular $P{=}O\cdots H{-}O$ hydrogen bonding, demonstrated before[4] for other 2-hydroxyalkylphosphonate esters. When the substrate was moved from chloroform-*d* to methanol-d_4, the population of the rotamer X_1 (or $X_1 + X_2$ for **2a**) decreased significantly (disruption of the intramolecular hydrogen bonding), although these conformations still prevailed in the solution.

The x-ray structures of both diastereomers were then determined; the perspective (Ortep[8]) views of the molecules are given in Figure 2 and selected molecular parameters are listed in Table 3. The first conclusion is that for both compounds the crystal structure corresponds exactly to that representing the most stable conformation in solution (X_1). The analysis of the torsion angles reveals almost ideal staggered conformation with the *trans* orientation of the PO_3Et_2/PNP groups, and the *gauche* relationship between the phosphoryl and the hydroxyl groups. This leads to the torsion angles between the vicinal hydrogens [H(9)—C(9)—C(12)—H(12)] achieving almost ideal values for the *gauche* (57°) or *trans* (175°) relationships; substituting these values into the Karplus equation[9] one arrives at vicinal coupling constants of 2·2 and 9·2 Hz, respectively, almost identical with the observed values. It must therefore be concluded that in chloroform both stereoisomers exist mostly as structures directly 'transferred' from the crystalline state. It should be additionally noted that the torsion angle between the phosphorus atom and the hydroxyl oxygen [P—C(9)—C(12)—O(22)] is in both cases smaller than 60° (*ca* 56°), indicating strong attraction between these two centres. The non-bonding distances between the P and the O(22) atoms (3·00, 2·95 Å) are both well below the sum of the corresponding van der Waals radii (3·30 Å). However, contrary to expectation, the observed strong attraction between the PO_3Et_2 and the OH groups is not a result of intramolecular hydrogen bonding. The intramolecular O(2)—O(22) and O(2)—H(22) distances are in both cases significantly greater than 3 Å, thus giving evidence for the absence of hydrogen bonding. The corresponding intermolecular distances (2·649 and 2·708 Å), on the other hand, correspond closely to the average oxygen— oxygen distance (2·671 Å) determined for various P—O—H—O—C hydrogen bonding systems.[10]

This type of interaction leads to the arrangement of

Table 2. Calculated vicinal coupling constants and the populations of rotamers X for phosphonates **2a** and **2b**

Phosphonate	$^3J(X_1)$ (Hz)	$^3J(X_2)$ (Hz)	$^3J(X_3)$ (Hz)	Solvent	$X_1 + X_2$ (%)	X_3 (%)
2a	1·51	3·34	9·52	$CDCl_3$	103	−3
				CD_3OD	88	12
					X_1 (%)	$X_2 + X_3$ (%)
2b	9·52	3·00	1·86	$CDCl_3$	99	1
				CD_3OD	74	26

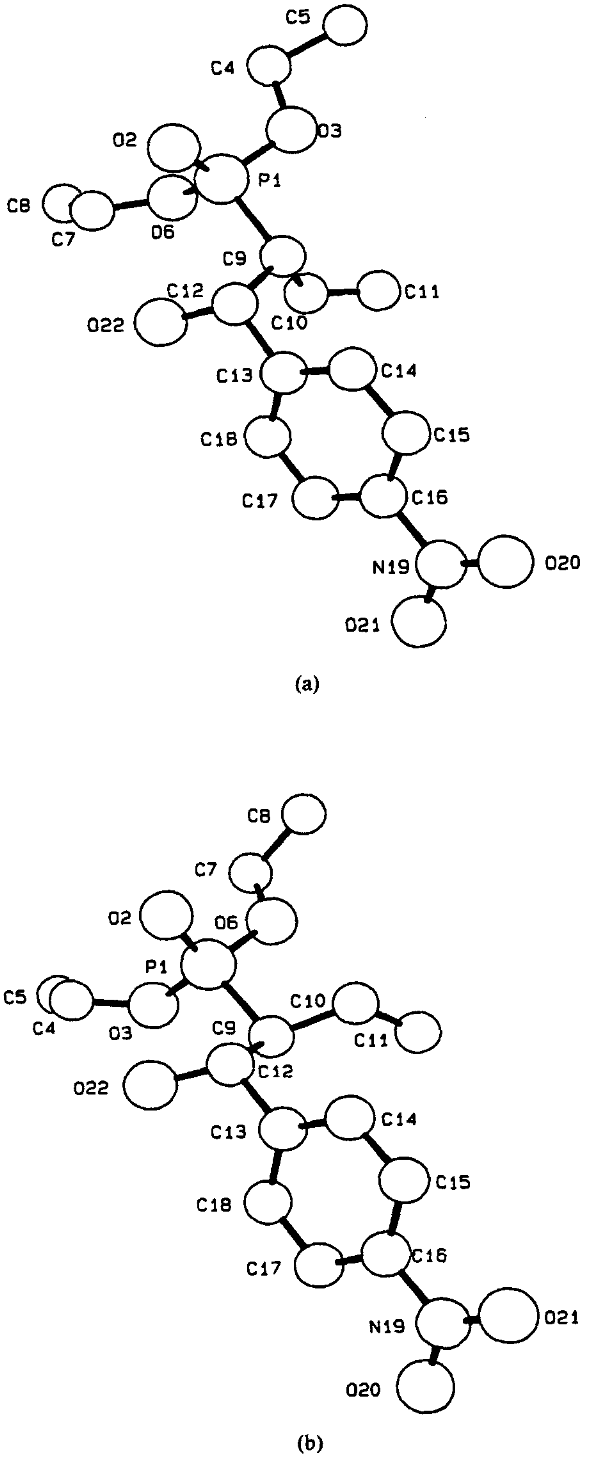


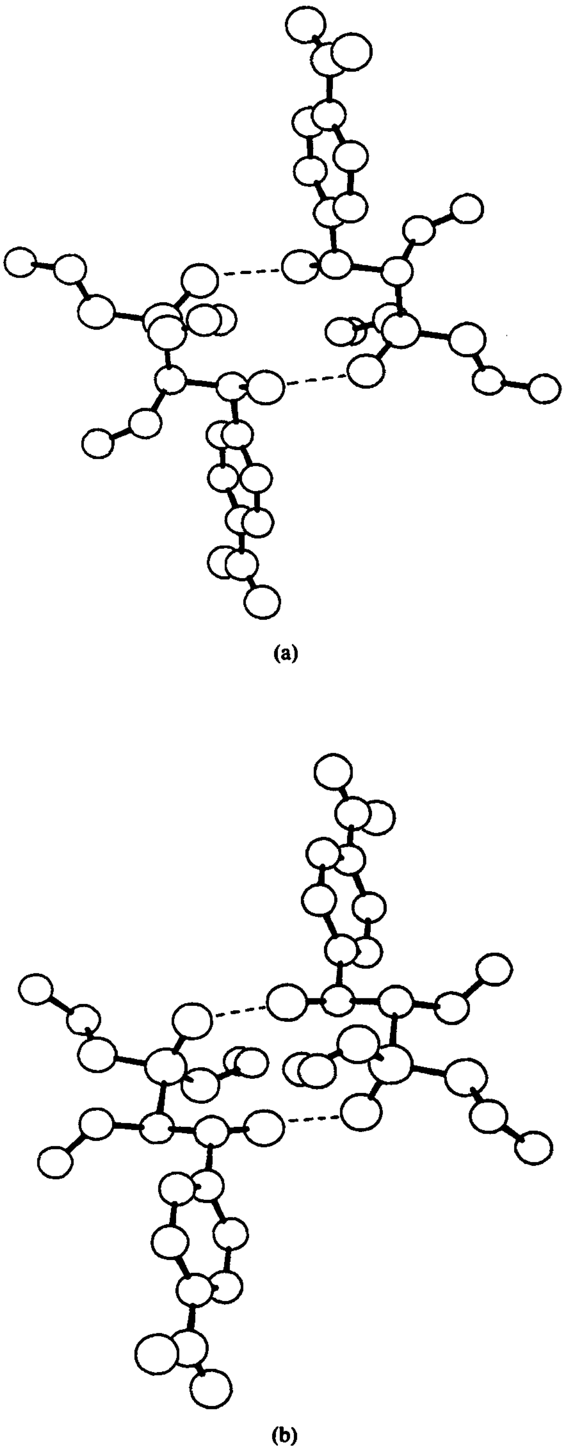
Figure 2. Perspective views with atomic numbering of (a) **2a** and (b) **2b**

Table 3. Selected molecular parameters of the diastereomers of diethyl 1-[(hydroxy)(*p*-nitrophenyl)methyl] prop-2-enylphosphonate

Parameter	**2a**	**2b**
Bond distances (Å):		
P=O(2)	1·474(6)	1·466(5)
P−C(9)	1·844(8)	1·824(7)
C(9)−C(12)	1·539(10)	1·580(9)
C(9)−C(10)	1·489(11)	1·535(10)
C(10)−C(11)	1·324(12)	1·328(10)
C(12)−C(13)	1·509(11)	1·513(9)
C(12)−O(22)	1·397(9)	1·377(8)
Torsion angles (°):		
P−C(9)−C(12)−C(13)	177(1)	179(1)
P−C(9)−C(12)−O(22)	55(1)	56(1)
P−C(9)−C(12)−H(12)	−64(1)	−63(1)
C(10)−C(9)−C(12)−C(13)	54(1)	−65(1)
C(10)−C(9)−C(12)−O(22)	−67(1)	173(1)
C(10)−C(9)−C(12)−H(12)	174(1)	54(1)
H(9)−C(9)−C(12)−C(13)	−62(1)	56(1)
H(9)−C(9)−C(12)−O(22)	176(1)	−66(1)
H(9)−C(9)−C(12)−H(12)	57(1)	175(1)
Non-bonded distances (Å):		
O(2)−O(22) intramolecular	3·230	3·179
O(2)−O(22) intermolecular	2·649	2·708
O(2)−H(22) intramolecular	3·452	3·540
O(2)−H(22) intermolecular	1·820	1·934
O(22)−P intramolecular	3·005	2·953

the molecules of **2** into the centrosymmetric, dimeric structures held by the pairs of the intermolecular hydrogen bonds (Figure 3). Our results demonstrate, *therefore, that when the molecules of* **2** *form crystals,* the requirements of the packing forces change the involvement of the P=O and O−H functional groups in the hydrogen bonding from intra- to intermolecular, still preserving the rigorous *gauche* orientation of these two groups in a single molecule. It is interesting that the pattern of the P=O ··· H−O−C hydrogen bonding in the solid state can change from system to system. For some tertiary 2-hydroxyalkylphosphine oxides Warren and co-workers observed both intramolecular[5] and intermolecular[11] interactions; in both cases the *gauche* relationship between the C_α−P and C_β−OH bonds was preserved. In the latter case[11] the intermolecular hydrogen bonding gave rise to a ribbon-like structure of a chain of molecules, each bonded to two others.

In the phosphonate system **2** we observe yet another type of hydrogen bond arrangement (dimeric structures), but the conformation of the molecule itself remains as in X_1, irrespective of the intermolecular relations. We propose to explain this conformational preference by postulating the presence of an additional (independent of the hydrogen bonding) stabilising effect, namely the n(p) → d donation of the non-bonding electrons of the hydroxyl oxygen to the vacant


(a)

(b)

Figure 3 Dimeric structures of (a) **2a** and (b) **2b**. Hydrogen bonding is indicated by dotted lines

d orbitals of phosphorus. A similar effect was suggested in the conformational analysis of 2-hydroxyalkyl sulphoxides[12] and also in our work on 2-alkoxyalkylphosphonates.[4] In conclusion, we believe that the phosphoryl function is capable of interacting with other functional groups via more than one mechanism, and should therefore be expected to play a significant role in determining the preferred conformation of an organophosphorus molecule, both in solution and in the solid state.

EXPERIMENTAL

The preparation and isolation of substrates **2a** and **2b** have been described elsewhere.[2] Both compounds gave NMR (^{1}H, ^{13}C and ^{31}P) and mass spectra in full agreement with the expected structure. NMR spectra were recorded on a Bruker AC 300 MHz spectrometer at a probe temperature of 30 °C. Chemical shifts are given in δ (ppm) relative to tetramethylsilane as an internal standard (^{1}H, ^{13}C) or 85% H_3PO_4 as an external standard (^{31}P). The solvents used for the analysis of the NMR spectra were chloroform-*d* (Uvasol, Merck) and methanol-d_4 (Uvasol, Merck), both dried over molecular sieves. The concentration of the substrates was 0·20 M.

Crystal structure determination. Colourless crystals of **2a** and **2b** were obtained by slow evaporation of solutions in hexane. Both compounds crystallized in the space group $P2_1/c$, with slightly different cell dimensions (Table 4). All diffraction measurements were performed at room temperature and the data were collected with an Enraf-Nonius CAD4 diffractometer using monochromated Mo Kα($\lambda = 0{\cdot}7107$ Å) radiation. The lattice constants were obtained from a least-squares fit of 25 centred reflections in the ranges $10° < \theta < 14°$ and $6°\theta < 11°$ for **2a** and **2b**, respectively. Data were corrected for Lorentz and polarisation effects. Absorption corrections were applied for **2b**. Intensity checks were carried out every hour and an orientation control every 200 reflections. Three standard reflections were used to check the orientation and crystal stability at regular intervals, and the decays during data collection were 0·6% and 2·9% (not corrected) for **2a** and **2b**, respectively.

The structures were solved by direct methods and refined anisotropically using a full matrix method ($1/\sigma^2F$ - weights) using SHELX76.[13] All hydrogen atoms, except the experimentally located and refined hydroxyl hydrogen [H(22)] were placed in calculated positions and were included in the refinement with a common isotropic temperature factor that converged to $U = 0{\cdot}308(9)$ Å^2 and $U = 0{\cdot}370(8)$ Å^2 for **2a** and **2b**, respectively. The O—C and C—C bond distances of the PO_3Et_2 groups were refined in a fixed mode by constraining the O—C bond distances to 1·420(1) Å and

Table 4. Crystallographic data acquisition and refinement details of compounds **2a** and **2b**

Data	**2a**	**2b**
Empirical formula	$C_{14}H_{20}NO_6P$	$C_{14}H_{20}NO_6P$
Molecular weight	329	329
Crystal dimensions (mm)	0·28 × 0·13 × 0·15	0·20 × 0·24 × 0·48
Space group	$P2_1/c$	$P2_1/c$
Cell dimensions:		
a(Å)	11·990(3)	11·632(3)
b(Å)	17·054(3)	17·967(6)
c(Å)	8·902(3)	8·401(4)
β(°)	105·25(2)	102·00(2)
Z	4	4
Volume (Å^3)	1756·1	1717·4
D(calc.) (g cm^{-3})	1·245	1·272
μ(cm^{-1})	1·41	1·44
T(°C)	25	24
F(000)	696	696
Scan type ($\omega : 2\theta$)	1 : 1	1 : 1
Scan range (θ°)	$3 \leqslant \theta \leqslant 27$	$3 \leqslant \theta \leqslant 27$
hkl-indices:		
h	0 : 11	0 : 10
k	0 : 21	0 : 22
l	− 15 : 15	− 14 : 14
Maximum scan speed (variable, °min^{-1})	Max. 3·30	Max. 3·30
Maximum scan time (s)	60	60
Scan angle (ω + 0·34 tanθ) (°)	0·55	0·62
Aperture size (mm)	1·3 × 4·0	1·3 × 4·0
Reflections collected	4203	4110
EAC correction factor:		
Maximum	none	0·999
Minimum	none	0·866
Average	–	0·946
Unique reflections used	1539 [$>3\sigma$(I)]	1824 [$>1\sigma$(I)]
R_{int}	0·0216	0·0143
Parameters refined	209	209
Max. positional shift/esd	0·135	0·127
Residual electron density (e Å^3):		
Maximum	0·41	0·57
Minimum	− 0·36	− 0·40
R	0·1047	0·1409
R_w	0·0612	0·0547

the C—C bond distances to 1.530(1) Å. This was necessary because the very high thermal motions of these atoms resulted in unrealistically short bonds.

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