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Energetic Study of the Disordered Solvent in the Crystal Structure of an Isoxazole Derivative

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Abstract

In the crystal structure of ethyl (*Z*)-3-{[3-(3,5-dichloro-2,4,6-trimethylphenyl)isoxazol-4-yl]-2-butenylidene}carbazate–ethyl acetate solvate, $C_{19}H_{21}Cl_2N_3O_3.0.34C_4H_8O_2$ ($R_1 = 0.072$, $wR_2 = 0.228$), the host molecules are linked by intermolecular $N—H\cdots N$ hydrogen bonds, giving rise to infinite channels which contain molecules of ethyl acetate. Packing potential energy calculations carried out for host–guest model crystals account for the disorder of the solvent molecules in the crystal state.

1. Introduction

In recent years the treatment of solvent molecules in cavities within a crystal structure has reached an important role. Of course, this is chiefly true in the case of biological macromolecules; however, the presence of (disordered) solvent in otherwise empty spaces of the crystal structure is becoming a frequent issue even in reports on small molecules. In fact, there are now different approaches at hand to face the problem and this acts as a challenge to crystallographers.

This report is part of a study on the reactions of aryl nitrile oxides with 1,2-diazepines and, more generally, on the competition between C═C and C═N bonds in [3 + 2] cycloadditions (Cadoni *et al.*, 1990, and references therein; Beltrame *et al.*, 1992).

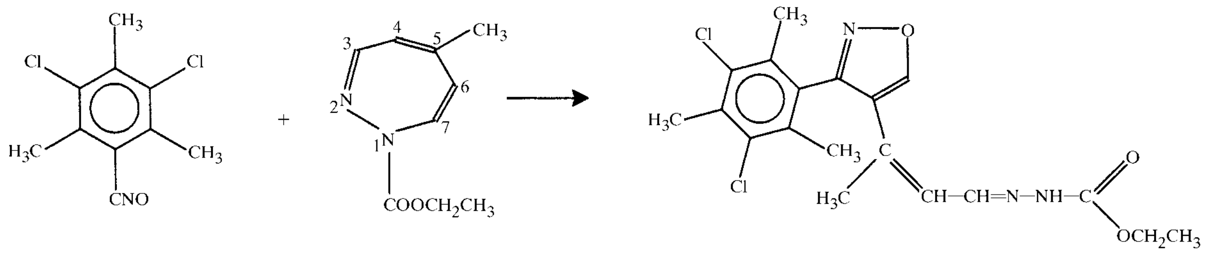
Compound (III) is a minor product of the reaction between 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide and ethyl 5-methyl-1,2-diazepine-1-carboxylate (see reaction scheme). The crystal structures of the main adduct and another by-product have been reported elsewhere (Beltrame *et al.*, 1993; Gelli *et al.*, 1994). The unexpected compound (III) is obtained from the addition of (I) to the C6═C7 bond of (II), with the opening of the diazepine ring and the formation of an isoxazole ring. Preliminary structural results have been published previously (Beltrame *et al.*, 1992).

The present work reports the crystal structure of (III) and an energetic study of the (disordered) guest molecules of solvent, which are present in channels created by the packing of the host molecules.

Table 1 lists complete experimental details.

2. Crystal structure solution

Crystals were obtained from a mixture of ethyl acetate and light petroleum ether (30:70 *v/v*). The crystal structure was solved by direct methods (*NRCVAX*; Gabe *et al.*, 1989). The *E* map showed 27 prominent peaks; the corresponding atoms were unambiguously identified during the refinement on the basis of bond distances and $U_{\rm iso}$ values. After some cycles of anisotropic refinement and the localization of most H atoms by means of ΔF syntheses, the R_1 index was 0.135 over



(I) (II) (III)

among other products

Table 1. *Experimental details*

Crystal data	
Chemical formula	$C_{19}H_{21}Cl_2N_3O_3.0.34C_4H_8O_2$
Chemical formula weight	440.1
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	8.230 (5)
b (Å)	35.82 (1)
c (Å)	8.042 (2)
β (°)	103.11 (3)
V (Å^3)	2309 (2)
Z	4
D_x (Mg m^{-3})	1.266
D_m (Mg m^{-3})	1.29
Density measured by	Flotation
Radiation type	Mo $K\alpha$
Wavelength (Å)	0.7107
No. of reflections for cell parameters	25
θ range (°)	14.3–17.5
μ (mm^{-1})	0.31
Temperature (K)	293
Crystal form	Thin plate
Crystal size (mm)	0.4 × 0.3 × 0.1
Crystal colour	Colourless
Data collection	
Diffractometer	Enraf–Nonius CAD-4*F*
Data collection method	ω–2θ scans
Absorption correction	ψ scan (North *et al.*, 1968)
$T_{\min}$	0.775
$T_{\max}$	1.00
No. of measured reflections	4029
No. of independent reflections	4029
No. of observed reflections	1762
Criterion for observed reflections	$F_o > 4\sigma(F_o)$
$\theta_{\max}$ (°)	25
Range of h, k, l	$0 \rightarrow h \rightarrow 9$ $0 \rightarrow k \rightarrow 42$ $-9 \rightarrow l \rightarrow 9$
No. of standard reflections	2
Frequency of standard reflections	Every 240 min
Refinement	
Refinement on	F^2
$R[F > 4\sigma(F)]$ (R_1)	0.072
$wR(F^2)$ (wR_2)	0.228
S	0.96
No. of reflections used in refinement	4029
No. of parameters used	245
H-atom treatment	H-atom parameters not refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1196P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	−0.04
$\Delta\rho_{\max}$ (e Å^{-3})	0.32
$\Delta\rho_{\min}$ (e Å^{-3})	−0.29
Extinction method	None
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

1846 reflections with $F_o > 4\sigma(F_o)$. However, two regions of residual electron density were observed in channels elongated along z at *ca* $x = 0$, $y = 0.25$ and $x = 0$, $y = 0.75$; this feature was ascribed to the presence of disordered solvent. Considering only the molecules of (III), the empty spaces remaining in the unit cell were evidenced by *CAVITY* (Mugnoli, 1992); a graphic representation of the results, as obtained through *ATOMS* (Dowty, 1993), is shown in Fig. 1.

The solvent molecules in the channels must partially overlap, owing to the presence of the c glide planes at $y = 0.25$ and at $y = 0.75$; however, the first five independent peaks obtained from the ΔF syntheses could be interpreted as a planar (partial) approximate model of a molecule of ethyl acetate. Its presence in the crystal was even supported by ^{1}H NMR data. In the subsequent refinement the treatment of the disordered solvent began using a rigid-body constraint for the five peaks described above. They were given an s.o.f. (site-occupancy factor) value fixed at 0.5 and individual $U_{\rm iso}$ variable parameters, which converged to values ranging between 0.10 and 0.17 Å^2 [$R_1 = 0.092$ over 1846 reflections with $F_o > 4\sigma(F_o)$, $wR_2 = 0.33$ over 4029 F_o^2].

3. Packing potential energy calculations

To have a better understanding of the solvent disorder we performed calculations of packing potential energy, PPE (*OPEC*; Gavezzotti, 1983), for an idealized host–guest system in the crystal state. A model crystal was constructed starting from the experimental coordinates of the host molecule, including 'idealized' guest molecules in the channels.† For the *OPEC* calculations the space group $P2_1$ was adopted rather than $P2_1/c$, in order to avoid overlap of solvent molecules; the asymmetric unit was made up of one guest molecule and a pair of host molecules, related by the symmetry operation c. Owing to the different origins in $P2_1/c$ and $P2_1$, the original set of coordinates had to be shifted by $0,0,-\frac{1}{4}$. Since the C26 atom in the host molecule is affected by disorder, the position corresponding to the higher site-occupation factor only was taken into account.

All intermolecular contacts were considered within 8 Å from atoms of the fundamental unit to a total of 37 surrounding asymmetric units. The PPE calculations were carried out by a grid-point exploration in the channel space, holding fixed the host molecules and moving the guest molecule as a rigid body; this approach is similar to that described by Candeloro De Sanctis *et al.* (1995).

The guest molecule, with its elongation axis parallel (P) or antiparallel (A) to the z direction, was initially positioned with its mass centre at the border of the channel, near to $x = 0$, $y = 0.25$. The variables were the

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† The model we considered for the molecule of ethyl acetate was that corresponding to the lowest energy conformation, as obtained from molecular mechanics (Burkert & Allinger, 1982) with the MM2 force field (*MacroModel*; Still *et al.*, 1989). A conformational search (Monte Carlo method, two rotatable bonds) and a subsequent energy minimization of all the geometries obtained gave 56 conformations within 25 kJ from the minimum. The minimum energy model showed a planar extended conformation for the isolated molecule.

Table 2. *Explored regions in packing potential energy calculations (see text)*

Each column contains a starting value, final value and increment for each parameter considered (fractional coordinates, °).

T_x	T_y	T_z	ROT$_x$	ROT$_y^P$	ROT$_y^A$	ROT$_z^P$	ROT$_z^A$
−0.05	0.0	0.0	0	−45	−30	−45	120
0.1	0.05	1.0	360	30	45	30	210
0.05	0.01	0.05	20	5	5	5	5

three translations T_x, T_y and T_z along *a*, *b* and *c*, respectively, and the three rotational parameters ROT$_x$, ROT$_y$ and ROT$_z$, with respect to the system of inertial axes of the guest molecule, the molecular *x* axis corresponding to the direction of elongation (Gavezzotti, 1983; see Table 2). As far as the packing energy is concerned, the *P* and *A* orientations of the 'guest model' are almost equivalent: among 97 model crystals having energies differing by less than 12 kJ mol^{-1} from the minimum, 42 are *P* and 55 are *A*. The corresponding values of translations and rotations specify a region in which the molecule of ethyl acetate can move easily without appreciable variation in the packing potential energy of the system. Relative PPE values for the ten lowest-energy models are reported in Table 3. These results can account for the occurrence of disorder for the solvent molecules; on the other hand, they do not provide unequivocal information on the orientation of the ethyl acetate molecule and its position within the channels.

4. Crystal structure refinement

To overcome this uncertainty, the final refinement of the structure was accomplished using the *BYPASS* procedure (van der Sluis & Spek, 1990), as implemented in the *SQUEEZE* routine (*PLATON*; Spek, 1990, 1994). According to this method, the contribution of the diffuse electron density in the disordered areas is referred back, by means of discrete Fourier transform, to the observed structure factors; the corrected data are then used in the subsequent refinement of the ordered part of the structure only (*SHELXL*93; Sheldrick, 1993). This procedure is repeated up to convergence. In the present case the total electron count over the solvent region results in 65 electrons per unit cell, corresponding to a host:guest ratio of 1:0.34.† The packing coefficient (Kitaigorodski, 1961) calculated on the basis of the same ratio of the molecular volumes (V_{host} = 352, V_{guest} = 88 Å^3) is C_K = 0.66; the corresponding value considering only the host molecules is C_K = 0.61.

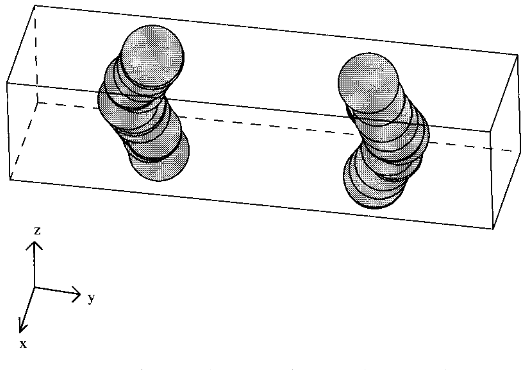

Fig. 1. A representation of the 'negative' of the crystal structure of (III). Spherical voids with radius r > 0.50 Å (*CAVITY*; Mugnoli, 1992) localized only spheres (1.96 < r < 2.26 Å) connected in continuous channels. They are shown in the diagram, where the origin of the unit cell is shifted at $\frac{1}{2}$, 0, 0.

Table 3. *Rigid-body parameters and relative packing potential energies (kJ mol^{-1}) for the ten model crystals of lowest energy*

Orientation	T_x	T_y	T_z	ROT$_x$	ROT$_y$	ROT$_z$	E
P	0.05	0.03	0.05	140	−20	−30	0.0
P	0.05	0.03	0.05	140	−25	−30	1.5
A	0.05	0.03	0.10	20	20	145	1.8
P	0.05	0.03	0.10	140	−20	−30	2.7
P	0.05	0.03	0.05	140	−20	−25	2.8
A	0.05	0.03	0.05	20	20	150	2.8
A	0.05	0.03	0.05	20	20	145	3.5
A	0.05	0.02	0.05	20	20	145	3.5
A	0.05	0.03	0.10	20	25	145	4.0
A	0.05	0.03	0.10	20	20	150	4.2

The (terminal) ethyl group is affected by disorder. During the refinement the atoms C26 and C26′ were treated isotropically, with the sum of their s.o.f.'s tied to unity [final values: 0.59 (4) and 0.41 (4), respectively; U(C26) = 0.085 (5), U(C26′) = 0.075 (6) Å^2]. The high displacement parameters of C27 indicated its trend to disordered behaviour, but the resolution of the data was not sufficient to consider the atom split over two distinct positions. The distances C26—C27 and C26′—C27 were constrained to refine to the same value, 1.35 (3) Å. Both bond angles O25—C26—C27 and O25—C26′—C27 converged to the same value, 107 (1)°. Most H atoms were located by ΔF syntheses. Those bonded to C19, C20, N22, C26, C26′ and C27, and one belonging to the C16 and C18 methyl groups, were placed in calculated positions.

In the last difference Fourier map, the highest $\Delta\rho$ values were found near the Cl atoms ($\Delta\rho_{\max}$ + 30.32 e Å^{-3}); the final reliability indexes were R_1 = 0.072 over 1762‡ $F_o > 4\sigma(F_o)$ and wR_2 = 0.228 on 4029 F_o^2 for 245 refined parameters, with a goodness-of-fit of 0.96.

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† This ratio is in fair agreement with the results of elemental analysis (experimental, calculated values for a 1:0.34 ratio: C 55.23, 55.53; H 5.09, 5.45; N 9.86, 9.54%) and of thermogravimetric measurements (about 7% loss of weight in the temperature range 343–483 K, corresponding to 0.35 molecules of ethyl acetate per host molecule).

‡ In the routine *SQUEEZE* (Spek, 1994) the observed intensities are corrected, while their s.u.'s preserve their original values. This causes a change in the number of structure factors above a given threshold.

Except for the disordered ethyl group, bond distances and angles for the isoxazole derivative (Fig. 2) are in good agreement with average values found in the literature (Allen *et al.*, 1987; Cambridge Structural Database, CSD, version 5.14; Allen & Kennard, 1993). The phenyl and isoxazole rings are planar within 0.006 and 0.004 Å, respectively, and, apart from the disordered tail, the side chain is also approximately planar (maximum deviation 0.05 Å). With respect to the isoxazole plane the dihedral angles of the phenyl ring and the side chain are 79.5 (3) and 50.2 (3)°, respectively. The C17═C19 and C20═N21 double bonds in the chain show *Z* and *E* configurations. Referring to the previous discussion on the disordered solvent, it is worthy of note that in the crystal the host molecules are connected in infinite chains through intermolecular N—H···N hydrogen bonds [N22···N21 3.179 (5) Å, N22—H22···N21 158°, N22—H22 1.00 Å, H22···N21 2.24 Å, N21 at $x, \frac{1}{2} - y, -\frac{1}{2} + z$], thus leaving empty channels along the *z* direction (Fig. 3). With respect to the sum of van der Waals radii, other intermolecular contacts are in the normal range, the shortest contact involving C16 and C26′ [C26′ at $x, \frac{1}{2} - y, -\frac{1}{2} + z$, 3.69 (2) Å]. All geometrical parameters were calculated using *PARST*95 (Nardelli, 1995).

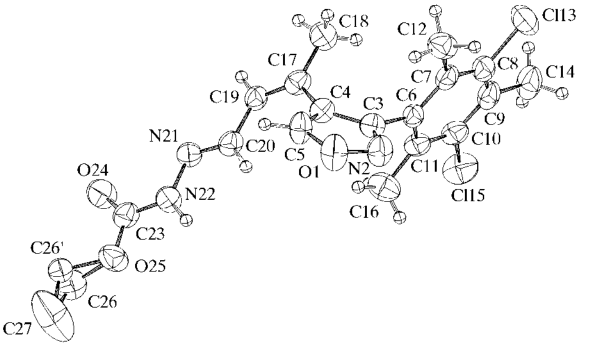

Fig. 2. *ORTEP* (Johnson, 1976) drawing of (III) with atom numbering. Displacement ellipsoids are drawn at the 40% probability level. C26 and C26′ were treated isotropically; H atoms are spheres of arbitrary radii. The H atoms of the ethyl group, affected by disorder, are omitted for clarity.

Table 4. *Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters* ($Å^2$)

$U_{\rm iso}$ for C26 and C26′, $U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U^{ij}a^ia^j\mathbf{a}_i.\mathbf{a}_j$ for others.

	x	*y*	*z*	$U_{\rm iso}/U_{\rm eq}$
O1	0.2756 (6)	0.1471 (1)	−0.1837 (4)	0.087 (2)
N2	0.3465 (6)	0.1118 (1)	−0.1460 (5)	0.077 (2)
C3	0.3725 (6)	0.1077 (1)	0.0191 (6)	0.057 (2)
C4	0.3226 (6)	0.1400 (1)	0.0982 (6)	0.056 (2)
C5	0.2631 (7)	0.1631 (1)	−0.0342 (6)	0.067 (2)
C6	0.4443 (6)	0.0732 (1)	0.1031 (6)	0.052 (2)
C7	0.3418 (7)	0.0416 (1)	0.1035 (6)	0.059 (2)
C8	0.4146 (8)	0.0102 (1)	0.1905 (7)	0.066 (2)
C9	0.5804 (8)	0.0083 (1)	0.2754 (7)	0.067 (3)
C10	0.6754 (7)	0.0398 (2)	0.2693 (6)	0.061 (2)
C11	0.6148 (7)	0.0724 (2)	0.1859 (6)	0.059 (2)
C12	0.1594 (8)	0.0423 (2)	0.0182 (7)	0.080 (3)
Cl13	0.2879 (3)	−0.02854 (4)	0.1949 (2)	0.0979 (8)
C14	0.6516 (9)	−0.0272 (2)	0.3725 (8)	0.092 (3)
Cl15	0.8862 (2)	0.03848 (5)	0.3723 (2)	0.0970 (7)
C16	0.7254 (8)	0.1040 (2)	0.1779 (8)	0.086 (3)
C17	0.3321 (6)	0.1473 (2)	0.2824 (6)	0.061 (2)
C18	0.2632 (8)	0.1177 (2)	0.3778 (7)	0.079 (2)
C19	0.4000 (6)	0.1788 (1)	0.3574 (6)	0.053 (2)
C20	0.4746 (6)	0.2080 (2)	0.2752 (6)	0.059 (2)
N21	0.5274 (5)	0.2379 (1)	0.3528 (5)	0.058 (1)
N22	0.5946 (6)	0.2632 (1)	0.2579 (5)	0.066 (2)
C23	0.6573 (7)	0.2953 (2)	0.3279 (7)	0.065 (2)
O24	0.6620 (6)	0.3051 (1)	0.4718 (5)	0.094 (2)
O25	0.7142 (5)	0.3156 (1)	0.2142 (5)	0.081 (2)
C26	0.813 (3)	0.3491 (3)	0.281 (1)	0.085 (5)
C26′	0.737 (4)	0.3556 (6)	0.259 (2)	0.075 (6)
C27	0.816 (2)	0.3713 (3)	0.146 (1)	0.203 (7)

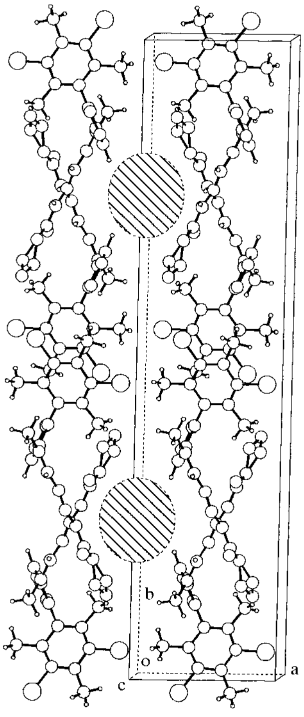

Fig. 3. *PLUTO* (Motherwell & Clegg, 1978) drawing of eight host molecules delimiting channels almost parallel to the *z* axis. The positions of the channels correspond to the hatched regions.

Final atomic parameters are listed in Table 4; selected geometric parameters are reported in Table 5.†

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† Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA0086). Services for accessing these data are described at the back of the journal.

Table 5. *Selected geometric parameters (Å, °)*

O1—N2	1.398 (6)	C20—N21	1.263 (6)
O1—C5	1.356 (7)	N21—N22	1.380 (6)
N2—C3	1.304 (7)	N22—C23	1.331 (7)
C3—C4	1.424 (7)	C23—O24	1.201 (7)
C4—C5	1.350 (7)	C23—O25	1.334 (7)
C8—Cl13	1.742 (6)	O25—C26	1.48 (2)
C10—Cl15	1.745 (5)	O25—C26′	1.48 (2)
C17—C19	1.340 (7)	C26—C27	1.35 (2)
C19—C20	1.448 (7)	C26′—C27	1.35 (3)
N2—O1—C5	107.5 (4)	C19—C20—N21	121.4 (5)
O1—N2—C3	106.6 (4)	C20—N21—N22	114.8 (4)
N2—C3—C6	121.3 (4)	N21—N22—C23	120.0 (4)
N2—C3—C4	111.5 (4)	N22—C23—O25	110.1 (5)
C4—C3—C6	127.2 (5)	N22—C23—O24	125.7 (5)
C3—C4—C17	129.2 (4)	O24—C23—O25	124.2 (5)
C3—C4—C5	103.6 (4)	C23—O25—C26′	114.1 (9)
C5—C4—C17	127.2 (4)	C23—O25—C26	116.2 (6)
O1—C5—C4	110.7 (4)	O25—C26—C27	107 (1)
C4—C17—C19	121.2 (4)	O25—C26′—C27	107 (1)
C17—C19—C20	125.5 (5)		
N2—C3—C6—C11	101.2 (6)	N21—N22—C23—O25	−179.6 (4)
C4—C3—C6—C7	99.6 (6)	N22—C23—O25—C26	−170.1 (8)
C4—C17—C19—C20	−2.0 (8)	N22—C23—O25—C26′	162 (1)
C17—C19—C20—N21	175.9 (5)	C23—O25—C26′—C27	172 (1)
C19—C20—N21—N22	−179.7 (4)	C23—O25—C26—C27	−162.0 (9)
N21—N22—C23—O24	−0.1 (8)		

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