

Structures of the Anticancer Compounds *N*-(2-Hydroxyethyl)-2-(3-nitro-1,2,4-triazol-1-yl)-acetamide (RB-6110) and 5-(1-Aziridinyl)-3-nitro-1-(3-oxo-1-butyl)-1,2,4-triazole (RB-6162)

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Abstract

RB-6110: $C_6H_9N_5O_4$, $M_r = 215.17$, monoclinic, $C2/c$, $a = 20.595$ (3), $b = 4.713$ (1), $c = 19.914$ (4) Å, $\beta = 110.69$ (1)°, $V = 1808.3$ Å³, $Z = 8$, $D_x = 1.588$ Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 0.838$ mm⁻¹, $F(000) = 675$, $T = 298$ K, final $R = 0.042$ for 1219 observed reflections with $I \geq 1.5\sigma(I)$.
 RB-6162: $C_8H_{11}N_5O_3$, $M_r = 225.21$, monoclinic, $P2_1/c$, $a = 7.515$ (1), $b = 14.758$ (2), $c = 9.813$ (1) Å, $\beta = 108.49$ (1)°, $V = 1032.1$ Å³, $Z = 4$, $D_x = 1.450$ Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 0.927$ mm⁻¹, $F(000) = 472$, $T = 298$ K, final $R = 0.042$ for 1113 observed reflections with $I \geq 1.5\sigma(I)$.
 RB-6110 and RB-6162 are 3-nitro-1,2,4-triazoles with potential application as anticancer agents. The nitro groups are in the plane of the aromatic triazole ring with dihedral angles of 1.2 (4) and 4.6 (4)°, respectively. The arizidine substituent of RB-6162 is almost perpendicular [dihedral angle 80.1 (4)°] to the triazole plane. Molecular-orbital calculations on RB-6162 have confirmed that this geometry is energetically favoured. The energy barrier to rotation about the triazole–aziridine bond has been determined as 51.5 (5) kJ mol⁻¹ by the dynamic NMR method.

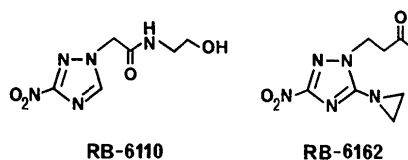
Introduction

The development of hypoxia-mediated compounds as anticancer agents has primarily focused upon nitroimidazoles, since these compounds show activity as hypoxia-selective radiosensitizers and cytotoxins (Adams, 1981; Adams & Stratford, 1986; Kennedy, 1987). Particular attention has recently been directed towards mixed-function nitro compounds which behave as monofunctional alkylating agents in aerobic cells but achieve bifunctional character following metabolic reduction ('bioactivation') under hypoxic conditions (Denny & Wilson, 1986; O'Neill, Jenkins *et al.*, 1987; O'Neill, McNeil & Jenkins, 1987).

Certain nitrotriazoles also show moderate hypoxic cell radiosensitization *in vitro* and *in vivo* (Astor,

Parham, Hall, Templeton & Hartog, 1983; Shibamoto *et al.*, 1986) and this observation has prompted the development of a series of 3-nitro-1,2,4-triazoles as formal ring aza-analogues of clinically useful nitroimidazoles. The synthesis and hypoxia-selective biological evaluation of these compounds will be described elsewhere.

As part of our studies of nitroheteroarenes with potential clinical application, we have determined the crystal structures of two new 3-nitro-1,2,4-triazoles, RB-6110 and RB-6162.



Experimental

RB-6110

Recrystallization from ethanol produced very pale yellow needle-like crystals, m.p. 358–359 K. A crystal of dimensions 0.4 × 0.1 × 0.05 mm was used. The space group was $C2/c$ (No. 15, monoclinic). Cell dimensions of a monoclinic I cell were obtained from least-squares refinement of 25 θ values ($9 < \theta < 28^\circ$) measured on an Enraf–Nonius diffractometer; Ni-filtered $\text{Cu } K\alpha$ radiation ($\lambda = 1.54178$ Å) was used. Intensity data were collected with an ω – 2θ scan technique and a max. scan time of 100 s per reflection, for $1.5 \leq \theta \leq 65^\circ$ and $0 \leq h \leq 23$, $0 \leq k \leq 5$, $-27 \leq l \leq 27$, after which the data and cell were translated to a standard monoclinic C setting; 3617 unique reflections were measured of which 1219 had $I \geq 1.5\sigma(I)$.

RB-6162

Recrystallization from ethyl acetate/triethylamine (99.5:0.5% *v/v*) produced very pale yellow rectangular crystals, m.p. 385–385.5 K. A crystal of dimensions 0.3 × 0.2 × 0.05 mm was used. The space group was $P2_1/c$ (No. 14, monoclinic). Cell dimensions

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were obtained from least-squares refinement of 25 θ values measured ($6 < \theta < 26^\circ$) on an Enraf-Nonius diffractometer; Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$) was used. Intensity data were collected with an ω - 2θ scan technique and a max. scan time of 100 s per reflection, for $1.5 \leq \theta \leq 65^\circ$ and $0 \leq h \leq 8$, $0 \leq k \leq 17$, $-11 \leq l \leq 11$; 1979 unique reflections were measured of which 1113 had $I \geq 1.5\sigma(I)$.

Three intensity standards were monitored every 60 min of X-ray exposure during the data collection for both structures and showed no statistically significant crystal decay. An empirical absorption correction was applied to both data sets (Walker & Stuart, 1983). For RB-6110 the minimum and maximum absorption correction factors used were 0.893 and 1.639, respectively; corresponding factors of 0.939 and 1.087 were applied for RB-6162. The structures were solved by direct methods with *MULTAN82* (Main *et al.*, 1982). H atoms were located in difference Fourier syntheses and their positional and isotropic thermal parameters refined on F by full-matrix least-squares methods, together with positional and anisotropic thermal parameters for the non-H atoms; apart from the H atoms on N12 and O15 of RB-6110 and C16 of RB-6162 where B 's were fixed at 5.0 \AA^2 . For RB-6110, the final R was 0.042 and wR was 0.049; for RB-6162, the final R was 0.042 and wR was 0.045 with $w = 1/[\sigma^2(F) + (0.04F)^2]^{1/2}$. The maximum Δ/σ was < 0.01 for both structures.

Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Calculations were performed on a VAX 11/750 computer using the *SDP* system (Frenz, 1980). The largest peaks in the final difference Fourier maps were within $\pm 0.2 e \text{ \AA}^{-3}$ for both structures.

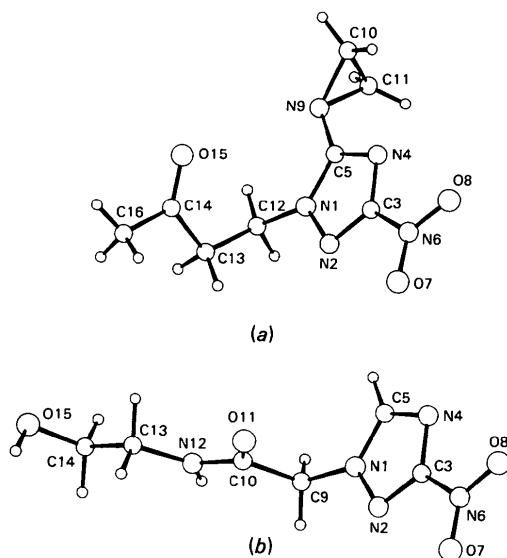


Fig. 1. Molecular structures of (a) RB-6162 and (b) RB-6110.

Table 1. *Non-hydrogen-atom positional and averaged thermal parameters, with e.s.d.'s in parentheses*

	x	y	z	$B_{eq}(\text{\AA}^2)^*$
RB-6110				
N1	0.14815 (8)	0.2825 (4)	-0.11511 (9)	2.59 (4)
N2	0.20488 (8)	0.4416 (4)	-0.10762 (9)	2.69 (4)
C3	0.1825 (1)	0.5931 (5)	-0.1666 (1)	2.45 (4)
N4	0.11706 (9)	0.5506 (4)	-0.21065 (9)	3.08 (4)
C5	0.0968 (1)	0.3508 (5)	-0.1758 (1)	3.25 (5)
N6	0.22642 (9)	0.8022 (4)	-0.1826 (1)	3.02 (4)
O7	0.28497 (8)	0.8323 (4)	-0.1395 (1)	4.78 (5)
O8	0.20197 (9)	0.9368 (4)	-0.23776 (9)	4.68 (4)
C9	0.1455 (1)	0.0937 (5)	-0.0585 (1)	2.99 (5)
C10	0.1165 (1)	0.2474 (5)	-0.0079 (1)	2.52 (4)
O11	0.10589 (9)	0.5033 (4)	-0.01263 (8)	4.05 (4)
N12	0.10194 (9)	0.0810 (4)	0.03806 (9)	2.89 (4)
C13	0.0744 (1)	0.1948 (5)	0.0907 (1)	3.20 (5)
C14	0.0561 (1)	-0.0409 (5)	0.1315 (1)	2.86 (5)
O15	0.02384 (7)	0.0679 (4)	0.17839 (8)	3.59 (4)
RB-6162				
N1	0.1699 (3)	0.8377 (1)	0.2958 (2)	2.64 (5)
N2	0.1765 (3)	0.8627 (2)	0.4306 (2)	3.03 (5)
C3	0.2207 (4)	0.9484 (2)	0.4292 (3)	2.90 (6)
N4	0.2430 (3)	0.9826 (1)	0.3095 (2)	3.01 (5)
C5	0.2099 (4)	0.9096 (2)	0.2258 (2)	2.64 (6)
N6	0.2421 (4)	1.0041 (2)	0.5552 (2)	3.95 (6)
O7	0.2082 (4)	0.9701 (2)	0.6571 (2)	6.23 (6)
O8	0.2951 (4)	1.0817 (1)	0.5524 (2)	6.13 (6)
N9	0.2132 (3)	0.9012 (1)	0.0858 (2)	3.22 (5)
C10	0.3924 (4)	0.9296 (2)	0.0644 (3)	3.96 (7)
C11	0.2289 (4)	0.9870 (2)	0.0138 (3)	3.87 (7)
C12	0.1297 (4)	0.7437 (2)	0.2475 (3)	3.20 (6)
C13	-0.0458 (4)	0.7082 (2)	0.2705 (3)	3.13 (7)
C14	-0.2246 (4)	0.7495 (2)	0.1776 (3)	3.20 (6)
O15	-0.2261 (3)	0.8035 (1)	0.0845 (2)	4.97 (5)
C16	-0.3973 (5)	0.7199 (2)	0.2064 (3)	4.59 (8)

* The equivalent isotropic thermal parameter, for atoms refined anisotropically, is defined by the equation:

$$1.333(a^2B_{11} + b^2B_{22} + c^2B_{33} + bCB_{23}\cos\alpha + aCB_{13}\cos\beta + abB_{12}\cos\gamma).$$

MNDO calculations were performed using the *AMPAC* semi-empirical molecular-orbital package (Quantum Chemistry Program Exchange No. 506, Dept. of Chemistry, Indiana University) in conjunction with the *GEMINI* (1988) molecular modelling program.

^1H NMR spectra were obtained with a Bruker AC250 FT spectrometer fitted with a programmable temperature facility. RB-6110 (CD_3OD , δ p.p.m.): 3.36 (t , $J = 5.6 \text{ Hz}$, 2H, CONHCH_2), 3.63 (t , $J = 5.6 \text{ Hz}$, 2H, CH_2OH), 5.11 (s , 2H, CH_2CO), 8.64 (s , 1H, arom- H). RB-6162 (d_6 -acetone, 298 K, δ p.p.m.): 2.19 (s , 3H, COCH_3), 2.56 (s , 4H, azir.), 3.23 (t , $J = 6.7 \text{ Hz}$, 2H, CH_2CO), 4.46 (t , $J = 6.7 \text{ Hz}$, 2H, arom- CH_2).

Discussion

The molecular structures of RB-6110 and RB-6162 are shown in Fig. 1. Atomic parameters and bond distances and angles are given in Tables 1 and 2.* The N(1)–N(2) triazole ring bond length [RB-6110,

* Lists of H-atom parameters, anisotropic thermal parameters and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51196 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Bond distances (Å), bond angles (°) for RB-6110 and RB-6162, and hydrogen-bond geometry for RB-6110

		RB-6110	RB-6162		
(a) Bond distances					
N1	N2	1.352 (2)	1.359 (3)	Common 3-nitro-1,2,4- triazole ring	
N1	C5	1.334 (2)	1.349 (3)		
N1	C12	—	1.467 (3)		
N1	C9	1.452 (2)	—		
N2	C3	1.311 (2)	1.309 (3)		
C3	N4	1.339 (2)	1.337 (3)		
C3	N6	1.447 (2)	1.450 (3)		
N4	C5	1.321 (3)	1.330 (3)		
C5	N9	—	1.388 (3)		
N6	O7	1.216 (2)	1.216 (3)		
N6	O8	1.213 (2)	1.215 (3)		
N9	C10	—	1.487 (4)		
N9	C11	—	1.473 (4)		
C10	C11	—	1.445 (4)		
C12	C13	—	1.502 (4)		
C13	C14	—	1.494 (4)		
C14	O15	—	1.211 (3)		
C14	C16	—	1.479 (5)		
C9	C10	1.524 (3)	—		
C10	O11	1.223 (2)	—		
C10	N12	1.318 (2)	—		
N12	C13	1.460 (2)	—		
C13	C14	1.500 (3)	—		
C14	O15	1.420 (2)	—		
(b) Bond angles					
N2	N1	C5	110.1 (2)	109.7 (2)	Common 3-nitro- 1,2,4- triazole ring
N2	N1	C9	121.5 (2)	—	
C5	N1	C9	128.1 (2)	—	
N2	N1	C12	—	120.8 (2)	
C5	N1	C12	—	129.5 (2)	
N1	N2	C3	100.8 (1)	100.5 (2)	
N2	C3	N4	117.3 (2)	118.5 (2)	
N2	C3	N6	121.3 (2)	119.8 (2)	
N4	C3	N6	121.4 (2)	121.6 (2)	
C3	N4	C5	101.2 (2)	100.7 (2)	
N1	C5	N4	110.6 (2)	110.5 (2)	
N1	C5	N9	—	120.7 (2)	
N4	C5	N9	—	128.7 (2)	
C3	N6	O7	117.7 (2)	118.2 (2)	
C3	N6	O8	117.7 (2)	117.6 (2)	
O7	N6	O8	124.6 (2)	124.2 (2)	
C5	N9	C10	—	114.6 (2)	
C5	N9	C11	—	115.3 (2)	
C10	N9	C11	—	58.4 (2)	
N9	C10	C11	—	60.3 (2)	
N9	C11	C10	—	61.3 (2)	
N1	C12	C13	—	112.5 (2)	
C12	C13	C14	—	115.4 (2)	
C13	C14	O15	—	121.4 (3)	
C13	C14	C16	—	115.9 (2)	
O15	C14	C16	—	122.7 (2)	
N1	C9	C10	110.7 (2)	—	
C9	C10	O11	121.3 (2)	—	
C9	C10	N12	114.5 (2)	—	
O11	C10	N12	124.1 (2)	—	
C10	N12	C13	121.5 (2)	—	
N12	C13	C14	110.6 (2)	—	
C13	C14	O15	110.7 (2)	—	

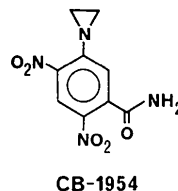
(c) Hydrogen-bond geometry for RB-6110

Symmetry translation	Angle (°)	Donor-acceptor distance (Å)	Acceptor-hydrogen distance (Å)	
$x, y-1, z$	O11...H121-N12	155.8 (1)	2.973 (4)	2.011 (2)
$x, 1-y, \frac{1}{2}+z$	N4...H151-O15	168.9 (1)	2.980 (3)	1.912 (2)

1.352 (2); RB-6162, 1.359 (3) Å] is similar to that found in 1,2,4-triazole [1.354 (3) Å] (Goldstein, Ladell & Abowitz, 1969) and 3-nitro-1,2,4-triazole [1.356 (5) Å] (Evrard, Durant, Michel & Fripiat, 1984) and is significantly shorter than an N—N single-bond length (1.470 Å) (Bryden, 1958).

The C—N bond lengths and angles in the triazole rings are not significantly different in the two compounds here, or compared to 3-nitro-1,2,4-triazole, and do not show the symmetrically comparable C—N bond lengths shown, for example, in 1-(mesityl-2-sulfonyl)-3-nitro-1,2,4-triazole (Kuroda, Sanderson & Neidle, 1982). The only significant difference between RB-6110 and RB-6162 concerning the triazole ring is a slight increase in N1—C5 and C5—N4 bond lengths (see Table 2) for RB-6162 owing to the aziridine substituent at C5. For both compounds the triazole ring is planar.

The nitro-group substituent at C3 shows no significant differences in bond lengths and angles in either structure compared with that in 5-(1-aziridinyl)-2,4-dinitrobenzamide (CB-1954) (Iball, Scrimgeour & Williams, 1975), 3-nitro-1,2,4-triazole, 1-(mesityl-2-sulfonyl)-3-nitro-1,2,4-triazole, 3-(1-methyl-4-nitro-5-imidazolyl)thio-1*H*-triazole (Dupont, Dideberg & Jamouille, 1984), and 1-(1-aziridinyl)-2,4,6-trinitrobenzene (CB-1943) (Barnes, Iball & Smith, 1977), or with tabulated N—O bond lengths of 1.14–1.21 (4) Å (*International Tables for X-ray Crystallography*, 1974). The nitro groups are in the plane of the triazole rings, the dihedral angles being 1.2 (4)° for RB-6110 and 4.6 (4)° for RB-6162. In RB-6110 the side chain at the 1-position has a planar amide group with the torsion angle O11—C10—N12—H121 being $-179.0 (4)^\circ$.



For RB-6162 the aziridine ring is nearly perpendicular to the five-membered triazole ring, the dihedral angle between the two least-squares planes being 80.1 (4)°. This differs markedly from the situation with CB-1954 (133.4°) and CB-1943 (127.5°) and reflects the different steric and mesomeric influences of the nitro group(s) and *ortho* substituents in these nitroarenes. The bond angles for the aziridine ring in RB-6162 also differ significantly from the equivalent angles in the CB structures.

	RB-6162 (°)	CB-1954 (°)	CB-1943 (°)
C5—N9—C10	114.6 (2)	122.7 (2)	122.7 (2)
C5—N9—C11	115.3 (2)	122.3 (2)	122.3 (2)
N9—C10—C11	60.3 (2)	59.5 (1)	59.5 (1)
N9—C11—C10	61.3 (2)	59.1 (1)	59.1 (1)
C10—N9—C11	58.4 (2)	61.3 (1)	61.3 (1)

The observation that the orientation of the aziridine ring is almost perpendicular to the triazole plane suggests that RB-6162 may have limited application as a hypoxia-selective cytotoxin. This is because deactivation of the alkylating aziridine moiety is critically dependent upon decreased electron density at N9

(Wilman & Connors, 1983) and hence effective conjugative π delocalization to the nitroarene. Bio-reduction of the nitro group would then result in conjugative electron release and, hence, restoration of alkylating function by the aziridine moiety (Denny & Wilson, 1986). MNDO calculations on RB-6162 revealed that the net charge on N9 is sensitive to rotation about the C5–N9 bond (Fig. 2a). The N1–C5–N9–C10 torsion angle in the crystal structure (124.1°) is close to the value of 147° which represents least charge delocalization from the N9 atom. The net atomic charges at the triazole ring N2 and N4 (but not N1) heteroatom positions are influenced in concert by rotation about the C5–N9 bond. The negative charges at N2 and N4 are decreased and increased, respectively, by *ca* 30% as the torsion angle is altered from 0° to the optimal 147° value. Such trends would not be wholly predicted by a simple delocalization model involving mesomeric interaction.

Calculations of enthalpies of formation (ΔH_f) for RB-6162 and for the same molecule with the N1 side chain replaced by a $-\text{CH}_3$ or $-\text{H}$ group (Figs. 2b,c,d, respectively) show that the crystallographic geometry is very energetically favoured. The enthalpic barrier to rotation predictably increases with increasing N1 functionality but the base of the enthalpy well is broad, suggesting that partial rotation may be facile. Justification for this conclusion is evident from the ^1H NMR spectrum for RB-6162 which reveals a temperature-dependent aziridine methylene resonance at δ 2.56 in d_6 -acetone solution (Fig. 3). This appears as a well resolved AB quartet showing magnetic non-equivalence ($J_{AB} = 2.75$ Hz, $\delta\nu = 4.09$ Hz or 0.016 p.p.m.) at 203 K, and as a sharp singlet at 298 K; coalescence at 235 ± 2 K corresponds (Bovey, 1969) to a ΔG^\ddagger of 51.5 ± 0.5 kJ mol $^{-1}$ for rotation about the

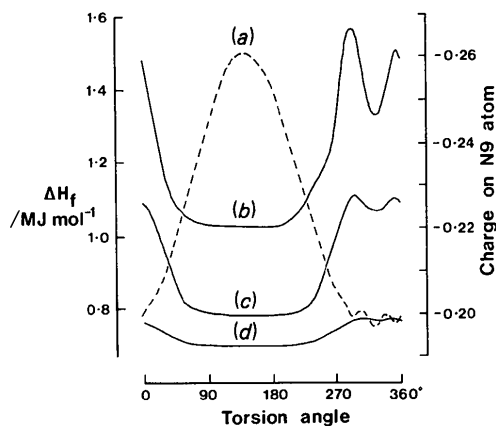


Fig. 2. Calculated (a) net charge on N9 atom and (b) enthalpy of formation (ΔH_f) for RB-6162 with variation of N1–C5–N9–C10 torsion angle. Torsion effects upon ΔH_f for RB-6162 with N1– CH_3 and N1–H functions are shown in (c) and (d), respectively.

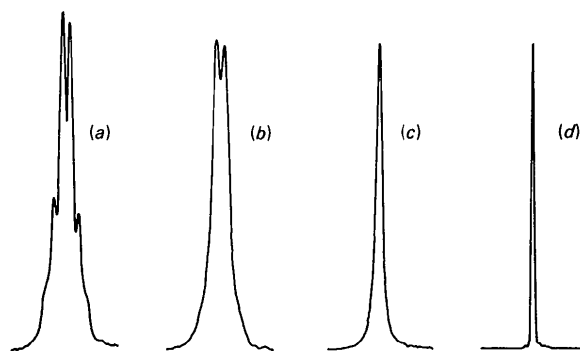


Fig. 3. Temperature-dependent ^1H NMR of the CH_2 (aziridine) resonance for RB-6162 at (a) 203, (b) 223, (c) 235 and (d) 298 K.

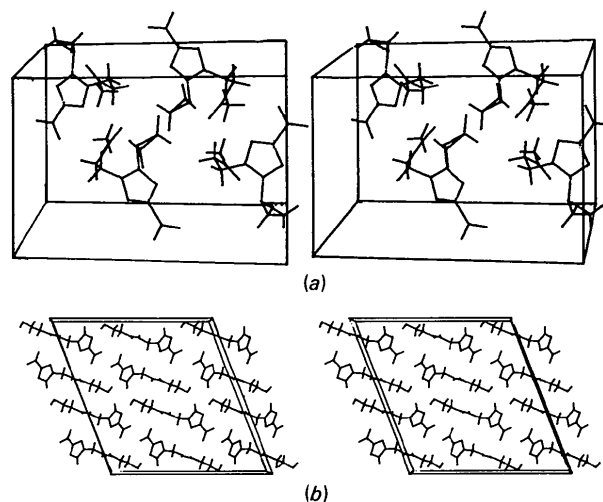


Fig. 4. Unit-cell packing diagrams for (a) RB-6162 (viewed down the a axis with b horizontal and c vertical) and (b) RB-6110 (viewed down the b axis with c horizontal and a vertical).

C5–N9 bond. ΔH^\ddagger and ΔS^\ddagger are notoriously difficult to resolve by the dynamic NMR method (Anderson & Pearson, 1975).

Crystal packing

Fig. 4 shows stereoviews of the packing diagrams for the molecules in their crystal lattices. RB-6110 has the ability to form two hydrogen bonds as described in Table 2(c).

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SHORT COMMUNICATIONS

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Practical resolution of the centrosymmetric/noncentrosymmetric ambiguity with the use of *E* statistics.*

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Abstract

An analysis of $\langle |E^2 - 1| \rangle$ values (calculated using all reflections) is reported for 167 data sets representing organic and organometallic compounds. It is shown that such an analysis may be a useful aid in assigning a centre of symmetry when a centrosymmetric/noncentrosymmetric (C/NC) ambiguity exists (for nontriclinic space groups). Distributions with average $\langle |E^2 - 1| \rangle$ values >0.82 are assigned as C space groups and those with values <0.82 are assigned to NC space groups. However, we note that often the only way of ensuring the correct choice of space group is a careful refinement of all options with particular emphasis on the possible role of disorder in the structure under investigation.

A commonly encountered problem in X-ray diffraction studies is the correct assignment of space group when a centrosymmetric/noncentrosymmetric (C/NC) ambiguity exists, e.g. $P1-\bar{P}1$, $Cc-C2/c$, and $Pna2_1-Pnam$ (Marsh,

1981, 1986). While much attention has been directed to the use of statistics to resolve the C/NC ambiguity we are not aware of a detailed analysis applied to a large number of structures. In this communication the average *E* statistics, $\langle |E^2 - 1| \rangle$, have been plotted for 167 data sets representing both organic and organometallic compounds obtained in these laboratories; see Fig. 1. The $\langle |E^2 - 1| \rangle$ values were calculated from the *SHELX76* (Sheldrick, 1976) program which calculates the *E* statistics as a function of $\sin(\theta)/\lambda$; reflections with $F \leq 0$ were ignored in the calculation. Only values from those regions which had a significant number of reflections (≥ 100 reflections) were used in the averaging process. Data were obtained routinely at room temperature on an Enraf-Nonius CAD-4 diffractometer utilizing mainly $MoK\alpha$ radiation; $\theta_{\max} = 22.5-30.0^\circ$. The data sets were corrected for Lorentz and polarization effects, and, in most cases, an analytical absorption correction was applied (Sheldrick, 1976). Generally the data sets were refined to final weighted residuals of $<6\%$ after weak reflections [usually the $I \geq 2.5\sigma(I)$ criterion of observability was applied] were omitted from the final refinement cycles.

Fig. 1(a) shows the distribution of $\langle |E^2 - 1| \rangle$ values for 167 data sets where the circles represent centrosymmetric

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