

Hydrogen-Bond Patterns in 1,4-Dihydro-2,3-quinoxalinediones: Ligands for the Glycine Modulatory Site on the NMDA Receptor

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(Received 10 January 1994; accepted 25 August 1995)

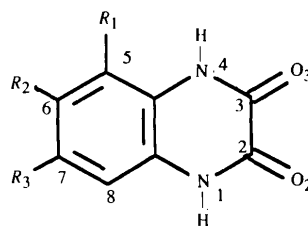
Abstract

The crystal structures of five 1,4-dihydro-2,3-quinoxalinediones, antagonists of the NMDA modulatory glycine binding site on the excitatory amino acid (EAA) receptor complex, have been determined: (I) 6,7-dinitro-1,4-dihydro-2,3-quinoxalinedione (DNQX); (II) 5,7-dinitro-1,4-dihydro-2,3-quinoxalinedione (MNQX); (III) 6-nitro-1,4-dihydro-2,3-quinoxalinedione hydrate; (IV) 6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione; (V) 5,7-dichloro-1,4-dihydro-2,3-quinoxalinedione dimethylformamide. The crystal structure of the most active compound (II) contains a unique intramolecular N—H...O(NO₂) hydrogen bond, which may be important for activity, as semiempirical calculations show that this bond is stable over a wide range of dihedral angles between the planes of the molecule and of the nitro group. In the other compounds the intermolecular hydrogen bonds connect molecules into three-dimensional networks. In compounds (I), (III) and (IV) head-to-tail π -stacking is found between molecules connected by a center of symmetry. The geometries of the hydrogen-bonded —NH—C=O fragments show evidence of π -cooperativity or resonance-assisted hydrogen bonding. Graph-set analysis of the hydrogen-bond patterns of quinoxalinedione derivatives shows a tendency to form two types of hydrogen-bonding motifs: a centrosymmetric dimeric ring and an infinite chain. Even though this pattern may be modified by the presence of additional hydrogen-bond acceptors and/or donors, as well as by solvent molecules, general similarities have been found. Comparison of all quinoxalinedione structures suggests that the hydrogen-bonding pattern necessary for the biological activity at the glycine binding site contains one donor and two acceptors.

1. Introduction

Quinoxalinedione (QD) derivatives have been found to be highly potent antagonists in the excitatory amino acid (EAA) neurotransmission system and to act by binding to

the glycine modulatory site of the NMDA (*N*-methyl-D-aspartic acid) receptor, as well as to other excitatory receptor subtypes (Honoré *et al.*, 1988; Randle *et al.*, 1992). EAA receptors are part of a supramolecular complex that forms a ligand-gated ion channel. The NMDA receptor requires both glutamate and glycine for activity; agonists and antagonists for these two sites are potential therapies for epilepsy, learning disorders and ischemic damage (Kemp & Lesson, 1993; Reynolds & Miller, 1990). For this reason, extensive structural studies of the QD derivatives have been performed. Structural analysis identifies three important features for biological action: the hydrogen-bonding pattern, the distribution of charge throughout the molecule and steric factors (Kubicki & Coddling, 1993; Kubicki, Kindopp, Capparelli & Coddling, 1992). To obtain further insight into these features, we have extended the studies to three nitro and two chloro derivatives. The nitro derivatives are important, because a small structural change from 6,7-dinitro-QD (DNQX; hereinafter the basic molecule, 1,4-dihydro-2,3-quinoxalinedione, will be referred to as QD) to 5,7-dinitro-QD (MNQX) reduces the affinity of the compounds for the nonNMDA receptors fourfold, but increases the antagonistic activity at the glycine site 30-fold (Watkins, Krogsgaard-Larsen & Honoré, 1989; Randle *et al.*, 1992). IC₅₀ values measure the concentration required to inhibit the binding of the natural ligand, glycine, by 50%. The IC₅₀ value for (I) is *ca* 4.5 μ M, for (II) is 0.14 μ M, for (III) is *ca* 27 μ M, and for (IV) and (V) is 4 μ M (Pullan, 1991). Thus, (II) is the most active of the



- (I) $R_2 = R_3 = \text{NO}_2$, $R_1 = \text{H}$
 (II) $R_1 = R_3 = \text{NO}_2$, $R_2 = \text{H}$
 (III) $R_2 = \text{NO}_2$, $R_1 = R_3 = \text{H}$
 (IV) $R_2 = R_3 = \text{Cl}$, $R_1 = \text{H}$
 (V) $R_1 = R_3 = \text{Cl}$, $R_2 = \text{H}$

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five compounds. We present X-ray crystallographic studies for DNQX (I), MNQX (II), 6-nitro-QD (III), 6,7-dichloro-QD (IV) and 5,7-dichloro-QD (V). Compound (III) crystallizes as the hydrate and (V) contains a dimethylformamide molecule in the crystal structure. The crystal structure of (III) has already been published (Stepień, 1981); our structure determination is of greater precision.

2. Experimental and results

Table 1 presents the crystal data, data collection and refinement details. The final atomic coordinates are given in Table 2 with the atomic labeling as given in the chemical diagram. The bond distances and angles are listed in Table 3.*

2.1. Crystal structures

2.1.1. Stacking. There are two important factors controlling the packing modes of the compounds: hydrogen bonds and π -stacking. Hydrogen-bond networks are present in all the structures; however, π -stacking is not. Crystals of (I), (III) and (IV) show head-to-tail π -stacking between molecules related by the center of symmetry. The distances between the mean plane of one molecule and the planes of neighboring centrosymmetrically related molecules are 3.414 (2) and 3.471 (2) Å in (I), 3.305 (2) and 3.232 (2) Å in (III), and 3.407 (2) and 3.335 (2) Å in (IV). In compound (V), the presence of a relatively bulky solvent molecule seems to disrupt π -stacking and prevent molecular overlap. Compound (II) is unique because it is the only QD derivative to crystallize in a noncentrosymmetric space group. There is no stacking in this structure, the dihedral angle between the planes of two symmetrically independent molecules is 88.45 (4)°.

2.1.2. Hydrogen bonding. As in other QD derivatives (Svensson, 1976; Grabowski, Stepień, Cygler & Wajzman, 1977; Stepień, 1981; Kubicki & Coddling, 1993) hydrogen bonds connect the molecules into the three-dimensional structures; the hydrogen-bond data, including some CH \cdots O interactions, are tabulated in Table 4. In the nitro derivatives (I, II and III) there are excess potential hydrogen-bond acceptors compared with the number of hydrogen-bond donors and thus some of the acceptors are not involved in any hydrogen bonds. (Throughout graph-set analysis, the terms donor and acceptor are used in reference to the hydrogen bonds, so a donor is an atom that donates a H atom and an acceptor is an atom that accepts a H atom; unfortunately, this convention is opposite to the usual nomenclature of

organic chemistry, which refers to donors and acceptors of a pair of electrons.) In (I), one of the N—H groups, N(1), acts as a donor for a strong and a weak hydrogen bond with both the O atoms, O(61) and O(62), of a nitro group of a neighboring molecule (see Fig. 1). The other N—H group, N(4), is hydrogen bonded to a carbonyl O atom, O(3), which is, in turn, also involved in a relatively strong C—H \cdots O interaction with C(5). The other carbonyl O atom is not involved in a hydrogen bond, but does take part in a number of close contacts with the nitro groups of neighboring molecules.

As shown Fig. 2, the water molecule in the crystal structure of (III) lowers the deficit of hydrogen-bond donors and the hydrogen-bonding pattern is closer to that found previously in QD structures (Kubicki & Coddling, 1993). Both N—H groups are linked to the carbonyl O atoms of the neighboring molecules, directly [N(4)—H(4)] or indirectly, through hydrogen bonds with the water molecule. The water molecule acts as an acceptor for an N—H \cdots O bond and as a donor for a two- and three-centered hydrogen bond with the carbonyl O atoms. In the previous structure of (III) (Stepień, 1981) a slightly different pattern of hydrogen bonds was found, perhaps because of the lower quality of the structure determination. The three-centered hydrogen bond connecting the water molecule with both carbonyl O atoms was not observed and thus the difference in the C—O bond lengths was discussed as due to the unequal number of accepted hydrogen bonds. This difference was 0.016 Å (not 0.018 Å, as stated in the paper) and is the same magnitude as the reported e.s.d.s for these bonds (also *ca* 0.016 Å).

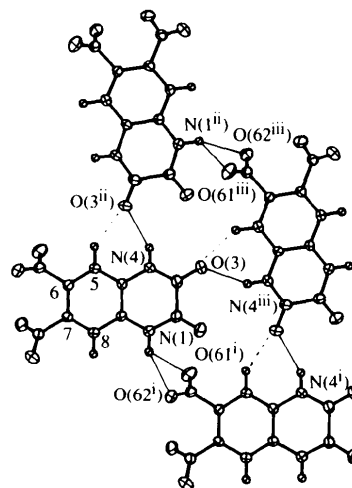


Fig. 1. Hydrogen-bond network for (I). Anisotropic ellipsoids are drawn at the 50% probability level, H atoms are represented as spheres of arbitrary radii (Johnson, 1976). Hydrogen bonds are drawn as thin lines and C—H \cdots O interactions are shown as dashed lines. Symmetry codes: (i) $x, 1+y, z$; (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$.

* Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: CR0473). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Experimental details*

	(I)	(II)	(III)	(IV)	(V)
Crystal data					
Chemical formula	C ₈ H ₄ N ₄ O ₆	C ₈ H ₄ N ₄ O ₆	C ₈ H ₅ N ₃ O ₄ ·H ₂ O	C ₈ H ₄ Cl ₂ N ₂ O ₂	C ₈ H ₄ Cl ₂ N ₂ O ₂ ·C ₃ H ₇ NO
Chemical formula weight	252.15	252.15	225.17	231.03	304.13
Cell setting	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Triclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> $\bar{1}$
<i>a</i> (Å)	8.4668 (3)	6.9774 (6)	7.4744 (9)	7.2066 (5)	6.1501 (4)
<i>b</i> (Å)	8.5533 (4)	13.083 (1)	11.9265 (9)	8.4502 (5)	8.3787 (4)
<i>c</i> (Å)	12.4657 (6)	20.401 (1)	10.4910 (5)	14.4709 (7)	13.7356 (10)
α (°)	90	90	90	90	107.407 (5)
β (°)	90.341 (3)	90	97.513 (7)	99.707 (5)	99.304 (6)
γ (°)	90	90	90	90	95.032 (4)
<i>V</i> (Å ³)	902.74 (7)	1862.3 (2)	927.2 (1)	868.62 (9)	659.50 (7)
<i>Z</i>	4	8	4	4	2
<i>D</i> _x (Mg m ⁻³)	1.855	1.799	1.613	1.767	1.532
Radiation type	Cu <i>K</i> α (Ni filter)	Cu <i>K</i> α (Ni filter)	Cu <i>K</i> α (Ni filter)	Cu <i>K</i> α (Ni filter)	Cu <i>K</i> α (Ni filter)
Wavelength (Å)	1.54178	1.54178	1.54178	1.54178	1.54178
No. of reflections for cell parameters	25	25	25	25	25
θ range (°)	19.58–43.61	20.69–53.86	27.28–50.81	16.83–44.30	32.68–53.83
μ (mm ⁻¹)	1.439	1.395	1.195	6.520	4.523
Temperature (K)	293 (2)	293 (2)	293 (2)	293 (2)	293 (2)
Crystal form	Prism	Prism	Prism	Elongated prism	Prism
Crystal size (mm)	0.34 × 0.22 × 0.16	0.30 × 0.20 × 0.12	0.44 × 0.18 × 0.18	0.54 × 0.40 × 0.26	0.40 × 0.25 × 0.20
Crystal color	Yellow	Pale yellow	Colorless	Orange	Pale yellow
Data collection					
Diffractometer	Enraf–Nonius CAD-4F	Enraf–Nonius CAD-4F	Enraf–Nonius CAD-4F	Enraf–Nonius CAD-4F	Enraf–Nonius CAD-4F
Data collection method	ω -2 θ	ω -2 θ	ω -2 θ	ω -2 θ	ω -2 θ
Absorption correction	None	None	None	Refined from ΔF (DIFABS; Walker & Stuart, 1983)	Refined from ΔF (DIFABS; Walker & Stuart, 1983)
<i>T</i> _{min}	–	–	–	0.267	0.31
<i>T</i> _{max}	–	–	–	0.461	0.49
No. of measured reflections	3846	2053	1852	1680	2724
No. of independent reflections	1854	2053	1852	1680	2724
No. of observed reflections	1730	2047	1843	1676	2599
Criterion for observed reflections	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)
<i>R</i> _{int}	0.0451	–	–	–	–
θ_{\max} (°)	74.87	74.83	74.74	74.69	74.76
Range of <i>h</i> , <i>k</i> , <i>l</i>	–8 → <i>h</i> → 10 –5 → <i>k</i> → 10 –15 → <i>l</i> → 15	0 → <i>h</i> → 8 0 → <i>k</i> → 16 0 → <i>l</i> → 25	–9 → <i>h</i> → 9 0 → <i>k</i> → 14 0 → <i>l</i> → 13	–9 → <i>h</i> → 8 0 → <i>k</i> → 10 0 → <i>l</i> → 15	–7 → <i>h</i> → 7 –10 → <i>k</i> → 10 0 → <i>l</i> → 17
No. of standard reflections	3	3	3	3	3
Frequency of standard reflections (s)	2000	2000	2000	2000	2000
Intensity decay (%)	<3	<1	<5	<1	<5
Refinement					
Refinement on	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)]	0.0314	0.0350	0.0506	0.0280	0.0425
<i>wR</i> (<i>F</i> ²)	0.0874	0.0922	0.1431	0.0771	0.1276
<i>S</i>	1.051	1.064	1.073	1.079	1.078
No. of reflections used in refinement	1851	2047	1845	1677	2723
No. of parameters used	180	358	174	144	195
H-atom treatment	All H-atom parameters refined	All H-atom parameters refined	All H-atom parameters refined	All H-atom parameters refined	Methyl H atoms fixed, all parameters refined for other H atoms
Weighting scheme	$w = 1/[\sigma^2(F^2) + (0.0296P)^2 + 0.2334P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F^2) + (0.0362P)^2 + 0.3565P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F^2) + (0.0667P)^2 + 0.4087P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F^2) + (0.4497P)]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F^2) + (0.0728P)^2 + 0.1510P]$, where $P = (F_o^2 + 2F_c^2)/3$
(Δ/σ) _{max}	0.001	0.001	0.001	0.001	0.001
$\Delta\rho_{\max}$ (e Å ⁻³)	0.242	0.205	0.184	0.305	0.321
$\Delta\rho_{\min}$ (e Å ⁻³)	–0.172	–0.154	–0.242	–0.279	–0.315
Extinction method	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)
Extinction coefficient	0.007 (1)	0.003 (1)	0.003 (1)	0.014 (1)	0.005 (1)
Source of atomic scattering factors	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)

Table 1 (cont.)

	(I)	(II)	(III)	(IV)	(V)
Computer programs					
Data collection	CAD-4F Software (Enraf-Nonius, 1989)	CAD-4F Software (Enraf-Nonius, 1989)	CAD-4F Software (Enraf-Nonius, 1989)	CAD-4F Software (Enraf-Nonius, 1989)	CAD-4F Software (Enraf-Nonius, 1989)
Cell refinement	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)
Data reduction	<i>ENDROC</i> (Rettig, 1978)	<i>ENDROC</i> (Rettig, 1978)	<i>ENDROC</i> (Rettig, 1978)	<i>ENDROC</i> (Rettig, 1978)	<i>ENDROC</i> (Rettig, 1978)
Structure solution	<i>SHELXS86</i> (Sheldrick, 1990)	<i>SHELXS86</i> (Sheldrick, 1990)	<i>SHELXS86</i> (Sheldrick, 1990)	<i>SHELXS86</i> (Sheldrick, 1990)	<i>SHELXS86</i> (Sheldrick, 1990)
Structure refinement	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)	<i>SHELXL93</i> (Sheldrick, 1993)

In compound (IV) (see Fig. 3) both of the N—H groups are hydrogen bonded to the carbonyl O atoms of neighboring molecules: N(4) forms two-centered and N(1) forms three-centered hydrogen bonds. The two-centered hydrogen bonds create centrosymmetric hydrogen-bonded dimers and the three-centered bonds form infinite chains along the [010] direction, additionally strengthened by a relatively strong C(8)—H(8)···O(3) interaction. The centrosymmetric dimer formation brings C(5)—H(5) and C(8)—H(8) into close proximity to the carbonyl O atoms of neighboring molecules. Additional stabilization of the lattice is gained from these C—H···O interactions (see Table 4).

In (V) the presence of a relatively bulky solvent molecule (dimethylformamide, DMF) and its hydrogen-bonding properties (strong hydrogen-bond acceptor, weak donor) produces a slightly different hydrogen-bonding pattern (see Fig. 4). One of the N—H groups, N(4), makes a centrosymmetric, hydrogen-bonded dimer with the neighboring molecule *via* N—H···O (from the QD molecule) hydrogen bonds. The other N—H group, N(1), acts as a donor for a hydrogen bond with the

carbonyl O atom of the DMF molecule. An additional weak C—H···O interaction between the solvent C—H group and the carbonyl O atom of the QD molecule closes a hydrogen-bonded ring, which includes two QD and two solvent molecules and is, in fact, a solvent-linked centrosymmetric dimer. Additional C—H···O interactions link the solvent methyl groups to the QD molecules.

Compound (II) has an intramolecular N(4)—H(4)···O(51) hydrogen bond which is unique (Fig. 5). The same N—H group is also involved in a weak hydrogen bond with a nitro-group O atom of the other molecule. The second N—H group, N(1)—H(1) in molecule *A* (unprimed atom labels) is hydrogen bonded to both of the carbonyl O atoms of the neighboring *B* molecule (primed atom labels) and N(1')—H(1') in molecule *B* is hydrogen bonded to the O(2) carbonyl O atom of the *A* molecule. There are also several C—H···O interactions in this structure.

To examine the importance of the intramolecular hydrogen bond in (II) we performed a series of semi-empirical calculations, using the AM1 Hamiltonian included in the *MOPAC5.0* package (Stewart, 1990;

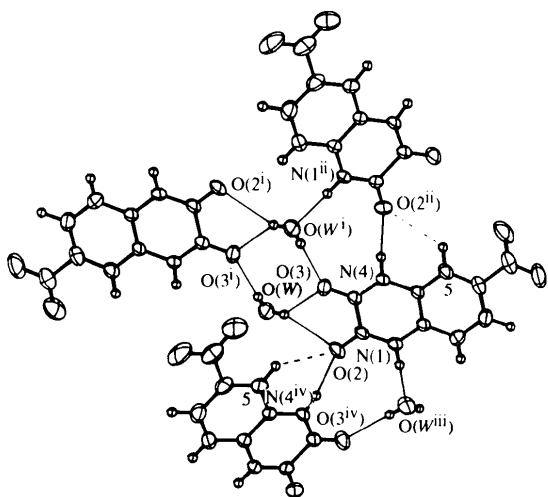


Fig. 2. Hydrogen-bond network for (III). Drawing prepared as in Fig. 1. Symmetry codes: (i) $-x, 1-y, 1-z$; (ii) $x-\frac{1}{2}, \frac{1}{2}-y, z-\frac{1}{2}$; (iii) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$.

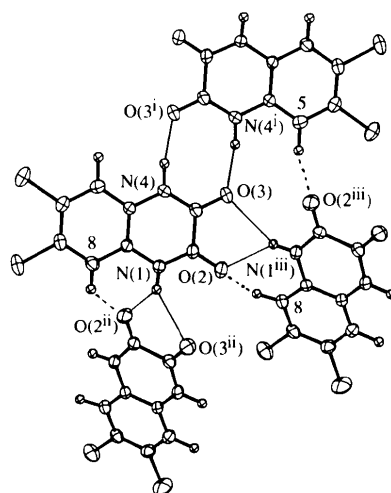


Fig. 3. Hydrogen-bond network for (IV). Drawing prepared as in Fig. 1. Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iii) $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$.

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)
$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j.$$

(I)	x	y	z	U_{eq}
N(1)	0.7743 (1)	0.2607 (1)	0.4651 (1)	0.031 (1)
C(2)	0.7091 (2)	0.3201 (1)	0.3737 (1)	0.029 (1)
O(2)	0.7255 (1)	0.4546 (1)	0.3455 (1)	0.041 (1)
C(3)	0.6107 (2)	0.2074 (1)	0.3065 (1)	0.030 (1)
O(3)	0.5446 (1)	0.2549 (1)	0.2263 (1)	0.043 (1)
N(4)	0.6002 (1)	0.0574 (1)	0.3413 (1)	0.028 (1)
C(4A)	0.6775 (1)	0.0011 (1)	0.4322 (1)	0.024 (1)
C(5)	0.6693 (1)	-0.1566 (1)	0.4598 (1)	0.025 (1)
C(6)	0.7498 (1)	-0.2070 (1)	0.5495 (1)	0.024 (1)
N(6)	0.7518 (1)	-0.3761 (1)	0.5687 (1)	0.028 (1)
O(61)	0.8808 (1)	-0.4401 (1)	0.5685 (1)	0.038 (1)
O(62)	0.6260 (1)	-0.4421 (1)	0.5791 (1)	0.045 (1)
C(7)	0.8372 (1)	-0.1047 (1)	0.6128 (1)	0.025 (1)
N(7)	0.9187 (1)	-0.1605 (1)	0.7093 (1)	0.028 (1)
O(71)	1.0455 (1)	-0.1011 (1)	0.7321 (1)	0.043 (1)
O(72)	0.8554 (1)	-0.2644 (1)	0.7608 (1)	0.040 (1)
C(8)	0.8458 (2)	0.0518 (1)	0.5865 (1)	0.027 (1)
C(8A)	0.7656 (1)	0.1047 (1)	0.4956 (1)	0.025 (1)
H(1)	0.829 (2)	0.328 (2)	0.5045 (14)	0.044 (5)
H(4)	0.545 (2)	-0.006 (2)	0.3036 (4)	0.044 (4)
H(5)	0.612 (2)	-0.2279 (18)	0.4153 (13)	0.037 (4)
H(8)	0.9042 (19)	0.1220 (18)	0.6282 (12)	0.034 (4)
(II)				
N(1)	0.3780 (4)	0.5046 (2)	0.0491 (1)	0.046 (1)
C(2)	0.4886 (4)	0.4946 (2)	0.1023 (1)	0.043 (1)
O(2)	0.6309 (4)	0.5453 (2)	0.1129 (1)	0.064 (1)
C(3)	0.4297 (4)	0.4142 (2)	0.1516 (1)	0.043 (1)
O(3)	0.5270 (4)	0.3968 (2)	0.1989 (1)	0.065 (1)
N(4)	0.2572 (4)	0.3667 (2)	0.1403 (1)	0.041 (1)
C(4A)	0.1438 (4)	0.3824 (2)	0.0862 (1)	0.036 (1)
C(5)	-0.0338 (4)	0.3342 (2)	0.0746 (1)	0.040 (1)
N(5)	-0.1218 (4)	0.2675 (2)	0.1241 (1)	0.050 (1)
O(51)	-0.0418 (4)	0.2564 (2)	0.1765 (1)	0.059 (1)
O(52)	-0.2758 (4)	0.2282 (2)	0.1095 (1)	0.081 (1)
C(6)	-0.1343 (4)	0.3494 (2)	0.0171 (2)	0.042 (1)
C(7)	-0.0609 (4)	0.4139 (2)	-0.0289 (1)	0.041 (1)
N(7)	-0.1633 (4)	0.4269 (2)	-0.0913 (1)	0.051 (1)
O(71)	-0.0977 (4)	0.4855 (2)	-0.1317 (1)	0.059 (1)
O(72)	-0.3103 (4)	0.3782 (2)	-0.0988 (1)	0.079 (1)
C(8)	0.1080 (5)	0.4670 (2)	-0.0197 (1)	0.042 (1)
C(8A)	0.2083 (4)	0.4517 (2)	0.0381 (1)	0.037 (1)
N(1')	0.0757 (4)	0.1904 (2)	0.3976 (1)	0.040 (1)
C(2')	0.0552 (4)	0.2742 (2)	0.4349 (1)	0.040 (1)
O(2')	0.1769 (3)	0.3055 (2)	0.4729 (1)	0.052 (1)
C(3')	-0.1340 (5)	0.3280 (2)	0.4295 (1)	0.040 (1)
O(3')	-0.1679 (4)	0.4014 (2)	0.4643 (1)	0.053 (1)
N(4')	-0.2612 (4)	0.2912 (2)	0.3848 (1)	0.040 (1)
C(4A')	-0.2248 (4)	0.2128 (2)	0.3421 (1)	0.033 (1)
C(5')	-0.3501 (4)	0.1809 (2)	0.2923 (1)	0.036 (1)
N(5')	-0.5401 (4)	0.2262 (2)	0.2841 (1)	0.044 (1)
O(51')	-0.5920 (3)	0.2924 (2)	0.3231 (1)	0.063 (1)
O(52')	-0.6407 (4)	0.1965 (2)	0.2390 (1)	0.060 (1)
C(6')	-0.3036 (4)	0.1039 (2)	0.2486 (1)	0.039 (1)
C(7')	-0.1279 (4)	0.0568 (2)	0.2561 (1)	0.040 (1)
N(7')	-0.0722 (4)	-0.0228 (2)	0.2094 (1)	0.049 (1)
O(71')	-0.1513 (4)	-0.0245 (2)	0.1561 (1)	0.068 (1)
O(72')	0.0497 (5)	-0.0836 (2)	0.2258 (1)	0.079 (1)
C(8')	-0.0023 (4)	0.0812 (2)	0.3056 (1)	0.038 (1)
C(8A')	-0.0494 (4)	0.1604 (2)	0.3482 (1)	0.035 (1)
H(1)	0.411 (6)	0.550 (3)	0.0218 (17)	0.065 (11)
H(4)	0.224 (5)	0.324 (3)	0.1694 (17)	0.054 (10)
H(6)	-0.258 (6)	0.312 (3)	0.0136 (17)	0.063 (11)
H(8)	0.146 (5)	0.515 (2)	-0.0540 (15)	0.047 (9)
H(1')	0.168 (6)	0.154 (3)	0.4016 (16)	0.051 (10)
H(4')	-0.353 (7)	0.323 (3)	0.379 (2)	0.077 (14)
H(6')	-0.391 (6)	0.085 (3)	0.2131 (17)	0.066 (11)
H(8')	0.115 (5)	0.048 (2)	0.3097 (15)	0.044 (9)
(III)				
N(1)	0.2601 (2)	0.0899 (1)	0.5628 (1)	0.036 (1)

Table 2 (cont.)

	x	y	z	U_{eq}
C(2)	0.2198 (2)	0.1984 (1)	0.5778 (1)	0.036 (1)
O(2)	0.2672 (2)	0.2522 (1)	0.6758 (1)	0.050 (1)
C(3)	0.1054 (2)	0.2560 (1)	0.4665 (2)	0.038 (1)
O(3)	0.0693 (2)	0.3552 (1)	0.4745 (1)	0.058 (1)
N(4)	0.0467 (2)	0.1915 (1)	0.3647 (1)	0.037 (1)
C(4A)	0.0934 (2)	0.0794 (1)	0.3517 (1)	0.033 (1)
C(5)	0.0283 (3)	0.0188 (2)	0.2424 (2)	0.039 (1)
C(6)	0.0763 (3)	-0.0925 (2)	0.2381 (2)	0.044 (1)
N(6)	0.0004 (3)	-0.1581 (2)	0.1264 (2)	0.056 (1)
O(61)	-0.1043 (3)	-0.1131 (2)	0.0432 (2)	0.087 (1)
O(62)	0.0460 (2)	-0.2568 (1)	0.1220 (2)	0.076 (1)
C(7)	0.1867 (3)	-0.1458 (2)	0.3364 (2)	0.047 (1)
C(8)	0.2508 (3)	-0.0845 (2)	0.4441 (2)	0.043 (1)
C(8A)	0.2029 (2)	0.0280 (1)	0.4529 (2)	0.034 (1)
O(1W)	0.0609 (3)	0.4850 (2)	0.7224 (2)	0.062 (1)
H(1)	0.325 (3)	0.058 (2)	0.629 (2)	0.053 (6)
H(4)	-0.031 (4)	0.219 (2)	0.305 (3)	0.064 (7)
H(5)	-0.047 (3)	0.0535 (19)	0.175 (2)	0.048 (5)
H(7)	0.218 (2)	-0.227 (2)	0.328 (2)	0.053 (6)
H(8)	0.320 (3)	-0.1185 (19)	0.517 (2)	0.049 (6)
H(1W1)	0.024 (4)	0.533 (3)	0.664 (3)	0.085 (9)
H(1W2)	0.085 (5)	0.433 (4)	0.691 (4)	0.109 (13)
(IV)				
N(1)	0.2200 (2)	0.6115 (2)	0.3410 (1)	0.028 (1)
C(2)	0.2628 (2)	0.7601 (2)	0.3183 (1)	0.029 (1)
O(2)	0.2363 (2)	0.8104 (2)	0.2383 (1)	0.045 (1)
C(3)	0.3547 (2)	0.8661 (2)	0.3977 (1)	0.028 (1)
O(3)	0.4073 (2)	0.9985 (1)	0.3791 (1)	0.041 (1)
N(4)	0.3771 (2)	0.8055 (2)	0.4849 (1)	0.028 (1)
C(4A)	0.3183 (2)	0.6545 (2)	0.5060 (1)	0.024 (1)
C(5)	0.3387 (2)	0.6024 (2)	0.5979 (1)	0.029 (1)
C(6)	0.2807 (2)	0.4515 (2)	0.6168 (1)	0.030 (1)
Cl(6)	0.3071 (1)	0.3886 (1)	0.7321 (1)	0.053 (1)
C(7)	0.2040 (2)	0.3518 (2)	0.5435 (1)	0.028 (1)
Cl(7)	0.1317 (1)	0.1618 (1)	0.5649 (1)	0.042 (1)
C(8)	0.1836 (2)	0.4031 (2)	0.4520 (1)	0.027 (1)
C(8A)	0.2402 (2)	0.5549 (2)	0.4328 (1)	0.023 (1)
H(1)	0.187 (3)	0.547 (3)	0.2966 (17)	0.047 (6)
H(4)	0.433 (3)	0.865 (3)	0.5294 (17)	0.043 (6)
H(5)	0.390 (3)	0.670 (3)	0.6472 (17)	0.047 (6)
H(8)	0.137 (3)	0.332 (3)	0.4008 (16)	0.045 (6)
(V)				
N(1)	-0.0382 (3)	0.8427 (2)	-0.2761 (1)	0.043 (1)
C(2)	0.1638 (3)	0.9373 (2)	-0.2504 (1)	0.044 (1)
O(2)	0.2407 (3)	1.0002 (2)	-0.3085 (1)	0.063 (1)
C(3)	0.2982 (3)	0.9629 (2)	-0.1414 (1)	0.041 (1)
O(3)	0.4809 (2)	1.0469 (2)	-0.1126 (1)	0.055 (1)
N(4)	0.2002 (3)	0.8875 (2)	-0.0812 (1)	0.039 (1)
C(4A)	-0.0106 (3)	0.7937 (2)	-0.1122 (1)	0.036 (1)
C(5)	-0.1060 (3)	0.7195 (2)	-0.0475 (1)	0.042 (1)
Cl(5)	0.0450 (1)	0.7436 (1)	0.0746 (1)	0.055 (1)
C(6)	-0.3159 (3)	0.6266 (2)	-0.0797 (2)	0.047 (1)
C(7)	-0.4317 (3)	0.6063 (2)	-0.1783 (2)	0.045 (1)
Cl(7)	-0.6944 (1)	0.4862 (1)	-0.2201 (1)	0.067 (1)
C(8)	-0.3454 (3)	0.6764 (2)	-0.2453 (1)	0.043 (1)
C(8A)	-0.1339 (3)	0.7709 (2)	-0.2111 (1)	0.038 (1)
O(15)	-0.3438 (3)	0.7529 (2)	-0.4622 (1)	0.068 (1)
C(15)	-0.4352 (4)	0.7870 (3)	-0.5381 (2)	0.051 (1)
N(15)	-0.6492 (3)	0.7458 (2)	-0.5794 (1)	0.048 (1)
C(115)	-0.7440 (5)	0.7869 (3)	-0.6714 (2)	0.069 (1)
C(125)	-0.7976 (4)	0.6555 (4)	-0.5353 (2)	0.068 (1)
H(1)	-0.115 (4)	0.825 (3)	-0.333 (2)	0.056 (7)
H(4)	0.288 (4)	0.907 (3)	-0.0212 (19)	0.047 (6)
H(6)	-0.380 (4)	0.580 (3)	-0.035 (2)	0.065 (7)
H(8)	-0.435 (4)	0.665 (3)	-0.3129 (19)	0.049 (6)
H(15)	-0.335 (5)	0.851 (4)	-0.572 (2)	0.078 (8)
H(11A)	-0.857 (2)	0.857 (2)	-0.6557 (5)	0.090
H(11B)	-0.809 (3)	0.6847 (4)	-0.7267 (5)	0.090
H(11C)	-0.6290 (7)	0.846 (2)	-0.6927 (9)	0.090
H(12A)	-0.899 (2)	0.5694 (16)	-0.5903 (2)	0.088
H(12B)	-0.881 (2)	0.7331 (6)	-0.4952 (13)	0.088
H(12C)	-0.7120 (5)	0.604 (2)	-0.4911 (12)	0.088

Table 3. Selected geometric parameters (Å, °)

(I)				(II)			
N(1)—C(2)	1.362 (2)	C(5)—H(5)	0.95 (2)	N(1)—C(2)	1.339 (4)	N(1')—C(2')	1.343 (4)
N(1)—C(8A)	1.3887 (14)	C(6)—C(7)	1.389 (2)	N(1)—C(8A)	1.390 (4)	N(1')—C(8A')	1.389 (3)
N(1)—H(1)	0.89 (2)	C(6)—N(6)	1.4662 (14)	N(1)—H(1)	0.84 (4)	N(1')—H(1')	0.80 (4)
C(2)—O(2)	1.211 (2)	N(6)—O(62)	1.213 (2)	C(2)—O(2)	1.214 (4)	C(2')—O(2')	1.220 (3)
C(2)—C(3)	1.522 (2)	N(6)—O(61)	1.222 (2)	C(2)—C(3)	1.513 (4)	C(2')—C(3')	1.501 (4)
C(3)—O(3)	1.213 (2)	C(7)—C(8)	1.380 (2)	C(3)—O(3)	1.202 (4)	C(3')—O(3')	1.216 (3)
C(3)—N(4)	1.357 (2)	C(7)—N(7)	1.464 (2)	C(3)—N(4)	1.374 (4)	C(3')—N(4')	1.362 (4)
N(4)—C(4A)	1.3919 (14)	N(7)—O(71)	1.219 (2)	N(4)—C(4A)	1.374 (3)	N(4')—C(4A')	1.369 (3)
N(4)—H(4)	0.85 (2)	N(7)—O(72)	1.2221 (14)	N(4)—H(4)	0.84 (3)	N(4')—H(4')	0.77 (5)
C(4A)—C(5)	1.394 (2)	C(8)—C(8A)	1.394 (2)	C(4A)—C(8A)	1.409 (4)	C(4A')—C(5')	1.405 (4)
C(4A)—C(8A)	1.399 (2)	C(8)—H(8)	0.93 (2)	C(4A)—C(5)	1.410 (4)	C(4A')—C(8A')	1.408 (3)
C(5)—C(6)	1.375 (2)			C(5)—C(6)	1.380 (4)	C(5')—C(6')	1.382 (4)
C(2)—N(1)—C(8A)	124.44 (11)	C(5)—C(6)—C(7)	121.61 (11)	C(5)—N(5)	1.470 (4)	C(5')—N(5')	1.462 (4)
C(2)—N(1)—H(1)	115.3 (11)	C(5)—C(6)—N(6)	116.55 (10)	N(5)—O(51)	1.215 (4)	N(5')—O(52')	1.221 (3)
C(8A)—N(1)—H(1)	120.2 (11)	C(7)—C(6)—N(6)	121.56 (10)	N(5)—O(52)	1.228 (4)	N(5')—O(51')	1.231 (3)
O(2)—C(2)—N(1)	123.43 (12)	O(62)—N(6)—O(61)	125.25 (11)	C(6)—C(5)—H(5)	121.3 (9)	C(6')—C(7')	1.380 (4)
O(2)—C(2)—C(3)	120.36 (12)	O(62)—N(6)—C(6)	117.89 (11)	C(6)—C(5)—C(4A)	118.61 (11)	C(6')—H(6')	0.98 (4)
N(1)—C(2)—C(3)	116.20 (10)	O(61)—N(6)—C(6)	116.79 (10)	C(6)—C(5)—H(5)	121.3 (9)	C(7)—C(8)	1.381 (4)
O(3)—C(3)—N(4)	123.30 (12)	C(8)—C(7)—C(6)	120.34 (11)	C(4A)—C(5)—H(5)	120.1 (10)	C(7)—N(7)	1.470 (4)
O(3)—C(3)—C(2)	119.32 (11)	C(8)—C(7)—N(7)	119.09 (11)			N(7)—O(72)	1.216 (4)
N(4)—C(3)—C(2)	117.37 (10)	C(6)—C(7)—N(7)	120.56 (10)			N(7)—O(71)	1.217 (4)
C(3)—N(4)—C(4A)	123.79 (11)	O(71)—N(7)—O(72)	124.71 (11)			C(8)—C(8A)	1.387 (4)
C(3)—N(4)—H(4)	117.4 (12)	O(71)—N(7)—C(7)	117.71 (10)			C(8)—H(8)	0.98 (3)
C(4A)—N(4)—H(4)	118.8 (12)	O(72)—N(7)—C(7)	117.58 (11)				
N(4)—C(4A)—C(5)	120.82 (11)	C(7)—C(8)—C(8A)	118.80 (11)				
N(4)—C(4A)—C(8A)	119.12 (10)	C(7)—C(8)—H(8)	121.3 (9)				
C(5)—C(4A)—C(8A)	120.06 (11)	C(8A)—C(8)—H(8)	119.9 (9)				
C(6)—C(5)—C(4A)	118.61 (11)	N(1)—C(8A)—C(8)	120.53 (11)				
C(6)—C(5)—H(5)	121.3 (9)	N(1)—C(8A)—C(4A)	118.88 (11)				
C(4A)—C(5)—H(5)	120.1 (10)	C(8)—C(8A)—C(4A)	120.58 (10)				
(III)				(IV)			
				N(1)—C(2)	1.347 (2)	C(4A)—C(8A)	1.395 (2)
				N(1)—C(8A)	1.389 (2)	C(5)—C(6)	1.383 (2)
				N(1)—H(1)	0.88 (3)	C(5)—H(5)	0.94 (2)
				C(2)—O(2)	1.224 (2)	C(6)—C(7)	1.394 (2)
				C(2)—C(3)	1.518 (2)	C(6)—Cl(6)	1.731 (2)
				C(3)—O(3)	1.218 (2)	C(7)—C(8)	1.377 (2)
				C(3)—N(4)	1.342 (2)	C(7)—Cl(7)	1.732 (2)
				N(4)—C(4A)	1.393 (2)	C(8)—C(8A)	1.388 (2)
				N(4)—H(4)	0.86 (3)	C(8)—H(8)	0.97 (2)
				C(4A)—C(5)	1.389 (2)		
				C(4A)—C(8A)	1.395 (2)		
				C(5)—C(6)	1.378 (3)		
				C(2)—N(1)—C(8A)	124.04 (13)	C(6)—C(5)—C(4A)	119.7 (2)
				C(2)—N(1)—H(1)	116 (2)	C(6)—C(5)—H(5)	120.4 (14)
				C(8A)—N(1)—H(1)	120 (2)	C(4A)—C(5)—H(5)	119.9 (14)
				O(2)—C(2)—N(1)	123.97 (14)	C(5)—C(6)—C(7)	120.1 (2)
				O(2)—C(2)—C(3)	118.7 (2)	C(5)—C(6)—Cl(6)	119.09 (13)
				N(1)—C(2)—C(3)	117.29 (13)	C(7)—C(6)—Cl(6)	120.84 (13)
				O(3)—C(3)—N(4)	123.9 (2)	C(8)—C(7)—C(6)	120.40 (14)
				O(3)—C(3)—C(2)	119.57 (14)	C(8)—C(7)—Cl(7)	121.14 (13)
				N(4)—C(3)—C(2)	116.46 (14)	C(7)—C(8)—C(8A)	119.68 (14)
				C(3)—N(4)—C(4A)	124.58 (13)	C(7)—C(8)—H(8)	120.5 (13)
				C(3)—N(4)—H(4)	119 (2)		
				C(4A)—N(4)—H(4)	116 (2)		
				C(5)—C(4A)—N(4)	121.03 (14)		
				C(5)—C(4A)—C(8A)	120.5 (2)		
				N(4)—C(4A)—C(8A)	118.48 (14)		
				C(6)—C(5)—C(4A)	117.7 (2)		
				C(6)—C(5)—H(5)	122.1 (14)		
				N(1)—C(2)	1.347 (2)	C(4A)—C(8A)	1.395 (2)
				N(1)—C(8A)	1.396 (2)	C(5)—C(6)	1.383 (2)
				N(1)—H(1)	0.85 (2)	C(5)—H(5)	0.94 (2)
				C(2)—O(2)	1.218 (2)	C(6)—C(7)	1.394 (2)
				C(2)—C(3)	1.518 (2)	C(6)—Cl(6)	1.731 (2)
				C(3)—O(3)	1.225 (2)	C(7)—C(8)	1.377 (2)
				C(3)—N(4)	1.346 (2)	C(7)—Cl(7)	1.732 (2)
				N(4)—C(4A)	1.394 (2)	C(8)—C(8A)	1.388 (2)
				N(4)—H(4)	0.86 (2)	C(8)—H(8)	0.97 (2)
				C(4A)—C(5)	1.386 (2)		
				C(2)—N(1)—C(8A)	124.06 (14)	C(6)—C(5)—C(4A)	119.7 (2)
				C(2)—N(1)—H(1)	118 (2)	C(6)—C(5)—H(5)	120.4 (14)
				C(8A)—N(1)—H(1)	118 (2)	C(4A)—C(5)—H(5)	119.9 (14)
				O(2)—C(2)—N(1)	123.5 (2)	C(5)—C(6)—C(7)	120.1 (2)
				O(2)—C(2)—C(3)	119.43 (14)	C(5)—C(6)—Cl(6)	119.09 (13)
				N(1)—C(2)—C(3)	117.04 (14)	C(7)—C(6)—Cl(6)	120.84 (13)
				O(3)—C(3)—N(4)	124.1 (2)	C(8)—C(7)—C(6)	120.40 (14)
				O(3)—C(3)—C(2)	119.0 (2)	C(8)—C(7)—Cl(7)	121.14 (13)
				N(4)—C(3)—C(2)	116.89 (13)	C(6)—C(7)—Cl(7)	121.14 (13)
				C(3)—N(4)—C(4A)	124.13 (14)	C(7)—C(8)—C(8A)	119.68 (14)
				C(3)—N(4)—H(4)	117 (2)	C(7)—C(8)—H(8)	120.5 (13)
				C(4A)—N(4)—H(4)	119 (2)	C(8A)—C(8)—H(8)	119.7 (13)
				C(5)—C(4A)—N(4)	120.96 (14)	C(8)—C(8A)—C(4A)	120.05 (14)
				C(5)—C(4A)—C(8A)	120.04 (14)	C(8)—C(8A)—N(1)	121.31 (14)
				N(4)—C(4A)—C(8A)	118.99 (14)	C(4A)—C(8A)—N(1)	118.63 (13)

Table 3 (cont.)

(V)			
N(1)—C(2)	1.347 (2)	C(7)—C(8)	1.379 (3)
N(1)—C(8A)	1.391 (2)	C(7)—Cl(7)	1.738 (2)
N(1)—H(1)	0.81 (3)	C(8)—C(8A)	1.392 (3)
C(2)—O(2)	1.213 (2)	C(8)—H(8)	0.97 (2)
C(2)—C(3)	1.531 (2)	O(1S)—C(1S)	1.225 (3)
C(3)—O(3)	1.211 (2)	C(1S)—N(1S)	1.317 (3)
C(3)—N(4)	1.361 (2)	C(1S)—H(1S)	1.03 (3)
N(4)—C(4A)	1.386 (2)	N(1S)—C(12S)	1.451 (3)
N(4)—H(4)	0.87 (3)	N(1S)—C(11S)	1.454 (2)
C(4A)—C(8A)	1.394 (2)	C(11S)—H(11A)	0.96
C(4A)—C(5)	1.398 (2)	C(11S)—H(11B)	0.96
C(5)—C(6)	1.379 (3)	C(11S)—H(11C)	0.96
C(5)—Cl(5)	1.726 (2)	C(12S)—H(12A)	0.96
C(6)—C(7)	1.378 (3)	C(12S)—H(12B)	0.96
C(6)—H(6)	0.94 (3)	C(12S)—H(12C)	0.96
C(2)—N(1)—C(8A)	125.2 (2)	C(7)—C(8)—C(8A)	118.2 (2)
C(2)—N(1)—H(1)	120 (2)	C(7)—C(8)—H(8)	119.9 (14)
C(8A)—N(1)—H(1)	114 (2)	C(8A)—C(8)—H(8)	121.8 (14)
O(2)—C(2)—N(1)	123.5 (2)	N(1)—C(8A)—C(8)	120.5 (2)
O(2)—C(2)—C(3)	120.1 (2)	N(1)—C(8A)—C(4A)	118.1 (2)
N(1)—C(2)—C(3)	116.4 (2)	C(8)—C(8A)—C(4A)	121.4 (2)
O(3)—C(3)—N(4)	123.4 (2)	O(1S)—C(1S)—N(1S)	124.5 (2)
O(3)—C(3)—C(2)	120.3 (2)	O(1S)—C(1S)—H(1S)	117 (2)
N(4)—C(3)—C(2)	116.4 (2)	N(1S)—C(1S)—H(1S)	119 (2)
C(3)—N(4)—C(4A)	124.1 (2)	C(1S)—N(1S)—C(12S)	121.0 (2)
C(3)—N(4)—H(4)	110 (2)	C(1S)—N(1S)—C(11S)	121.2 (2)
C(4A)—N(4)—H(4)	125 (2)	C(12S)—N(1S)—C(11S)	117.8 (2)
N(4)—C(4A)—C(8A)	119.7 (2)	N(1S)—C(11S)—H(11A)	109.47 (14)
N(4)—C(4A)—C(5)	122.3 (2)	N(1S)—C(11S)—H(11B)	109.47 (12)
C(8A)—C(4A)—C(5)	118.0 (2)	H(11A)—C(11S)—H(11B)	109.5
C(6)—C(5)—C(4A)	121.5 (2)	N(1S)—C(11S)—H(11C)	109.47 (13)
C(6)—C(5)—Cl(5)	119.68 (14)	H(11A)—C(11S)—H(11C)	109.5
C(4A)—C(5)—Cl(5)	118.9 (2)	H(11B)—C(11S)—H(11C)	109.5
C(7)—C(6)—C(5)	118.7 (2)	N(1S)—C(12S)—H(12A)	109.47 (12)
C(7)—C(6)—H(6)	121 (2)	N(1S)—C(12S)—H(12B)	109.47 (13)
C(5)—C(6)—H(6)	120 (2)	H(12A)—C(12S)—H(12B)	109.5
C(6)—C(7)—C(8)	122.3 (2)	N(1S)—C(12S)—H(12C)	109.47 (13)
C(6)—C(7)—Cl(7)	118.8 (2)	H(12A)—C(12S)—H(12C)	109.5
C(8)—C(7)—Cl(7)	118.9 (2)	H(12B)—C(12S)—H(12C)	109.5

Dewar, Zebisch, Healy & Stewart, 1985) to calculate the stability of the molecule at various fixed values of the nitro-group torsion angle. These calculations were designed to probe the relative stabilization of the intramolecular hydrogen bond. The calculation was

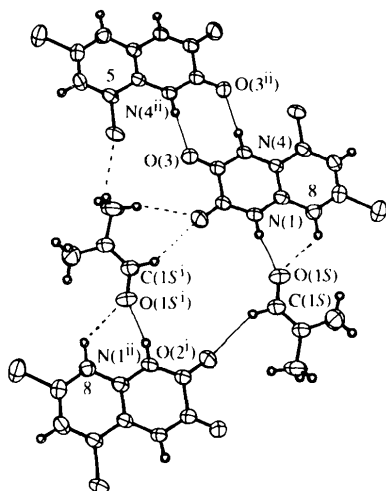


Fig. 4. Hydrogen-bond network for (V). Drawing prepared as in Fig. 1. Symmetry codes: (i) $-x, 2-y, -1-z$; (ii) $1-x, 2-y, -z$.

Table 4. Hydrogen-bond data ($\text{\AA}, ^\circ$)

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
(I)				
N(1)—H(1) \cdots O(61 ⁱ)	0.88 (2)	2.18 (2)	3.002 (1)	154 (1)
N(1)—H(1) \cdots O(62 ⁱ)	0.88 (2)	2.77 (2)	3.175 (1)	109 (1)
N(4)—H(4) \cdots O(3 ⁱⁱ)	0.85 (2)	2.21 (2)	2.982 (1)	150 (1)
C(5)—H(5) \cdots O(3 ⁱⁱ)	0.95 (2)	2.21 (2)	3.031 (2)	144 (1)
C(5)—H(5) \cdots O(72 ⁱⁱⁱ)	0.95 (2)	2.83 (2)	3.023 (2)	92 (1)
C(8)—H(8) \cdots O(71 ^{iv})	0.93 (2)	2.97 (2)	3.841 (2)	156 (1)
C(8)—H(8) \cdots O(72 ^{iv})	0.93 (2)	2.64 (2)	3.527 (2)	159 (1)
(II)				
N(1)—H(1) \cdots O(2 ^v)	0.84 (4)	2.23 (4)	2.956 (4)	144 (3)
N(1)—H(1) \cdots O(3 ^v)	0.84 (4)	2.24 (4)	2.932 (4)	140 (3)
N(4)—H(4) \cdots O(51)	0.85 (4)	2.06 (4)	2.642 (2)	125 (3)
N(4)—H(4) \cdots O(52 ^{vi})	0.85 (4)	2.39 (3)	3.086 (4)	140 (3)
C(8)—H(8) \cdots O(2 ^v)	0.98 (3)	2.71 (3)	3.337 (4)	122 (2)
C(8)—H(8) \cdots O(71 ^{vii})	0.98 (3)	2.52 (3)	3.335 (4)	141 (2)
N(1')—H(1') \cdots O(2 ⁱⁱ)	0.80 (4)	2.02 (4)	2.800 (4)	163 (4)
N(4')—H(4') \cdots O(51')	0.77 (5)	2.06 (5)	2.628 (4)	131 (4)
N(4')—H(4') \cdots O(71 ^{viii})	0.77 (5)	2.54 (4)	3.101 (4)	131 (4)
C(6')—H(6') \cdots O(52)	0.98 (4)	2.94 (4)	3.278 (4)	101 (2)
C(6')—H(6') \cdots O(71 ^{ix})	0.98 (4)	2.38 (4)	3.357 (4)	172 (3)
C(8')—H(8') \cdots O(2 ⁱⁱ)	0.93 (4)	2.37 (3)	3.114 (4)	136 (3)
(III)				
N(1)—H(1) \cdots O(1W ^x)	0.88 (2)	1.89 (2)	2.765 (2)	173 (2)
N(4)—H(4) \cdots O(2 ^{xi})	0.86 (3)	1.92 (3)	2.768 (2)	167 (3)
O(1W1)—H(1W1) \cdots O(3 ^{xii})	0.86 (3)	2.02 (3)	2.885 (2)	178 (2)
C(5)—H(5) \cdots O(2 ^{xi})	0.94 (2)	2.70 (2)	3.377 (2)	129 (2)
C(5)—H(5) \cdots O(61 ^{xiii})	0.94 (2)	2.77 (2)	3.318 (3)	117 (2)
C(8)—H(8) \cdots O(62 ^{xiv})	0.96 (2)	2.41 (2)	3.295 (3)	154 (2)
O(1W)—H(1W2) \cdots O(2)	0.74 (4)	2.56 (4)	3.244 (2)	154 (3)
O(1W)—H(1W2) \cdots O(3)	0.74 (4)	2.44 (4)	3.034 (2)	138 (4)
(IV)				
N(1)—H(1) \cdots O(2 ^{xv})	0.84 (2)	2.16 (2)	2.831 (2)	136 (2)
N(1)—H(1) \cdots O(3 ^{xvi})	0.84 (2)	2.55 (2)	3.304 (2)	149 (2)
N(4)—H(4) \cdots O(3 ^{xvii})	0.86 (2)	1.98 (2)	2.829 (2)	171 (2)
C(5)—H(5) \cdots O(2 ^{xviii})	0.94 (2)	2.62 (2)	3.304 (2)	130 (2)
C(8)—H(8) \cdots O(2 ^{xix})	0.97 (2)	2.35 (2)	3.011 (2)	125 (2)
(V)				
N(1)—H(1) \cdots O(1S)	0.81 (3)	1.98 (2)	2.772 (2)	169 (3)
N(4)—H(4) \cdots O(3 ^{xviii})	0.87 (2)	2.03 (2)	2.914 (2)	175 (2)
C(8)—H(8) \cdots O(1S)	0.97 (2)	2.51 (3)	3.230 (3)	131 (2)
C(1S)—H(1S) \cdots O(2 ^{xix})	1.03 (4)	2.46 (4)	3.425 (3)	157 (2)
C(11S)—H(11A) \cdots O(2 ^{xx})	0.96 (1)	2.78 (3)	3.683 (4)	158
C(11S)—H(11B) \cdots Cl(5 ^{xxi})	0.96 (1)	2.93 (4)	3.417 (3)	112
C(11S)—H(11C) \cdots O(2 ^{xxii})	0.96 (1)	2.61 (4)	3.527 (4)	160
C(12S)—H(12B) \cdots O(2 ^{xxiii})	0.96 (1)	2.79 (1)	3.514 (3)	133

Symmetry codes: (i) $x, 1+y, z$; (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iii) $x, -\frac{1}{2}-y, z-\frac{1}{2}$; (iv) $2-x, \frac{1}{2}+y, \frac{1}{2}-z$; (v) $\frac{1}{2}-x, 1-y, z-\frac{1}{2}$; (vi) $1+x, y, z$; (vii) $\frac{1}{2}+x, \frac{1}{2}-y, -z$; (viii) $-\frac{1}{2}-x, 1-y, \frac{1}{2}+z$; (ix) $x-\frac{1}{2}, \frac{1}{2}-y, -z$; (x) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (xi) $x-\frac{1}{2}, \frac{1}{2}-y, z-\frac{1}{2}$; (xii) $-x, 1-y, 1-z$; (xiii) $-x, -y, -z$; (xiv) $\frac{1}{2}+x, -\frac{1}{2}-y, \frac{1}{2}+z$; (xv) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (xvi) $1-x, 2-y, 1-z$; (xvii) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; (xviii) $1-x, 2-y, -z$; (xix) $-x, 2-y, -1-z$; (xx) $-1-x, 2-y, -1-z$; (xxi) $x-1, y, z-1$; (xxii) $x-1, y, z$.

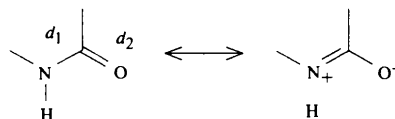
performed for the 5- and 7-nitro groups separately. The dihedral angle was stepped from 0 to 90° in increments of 10° and the rest of the structure was optimized at each step. The stabilizing effect of the intramolecular hydrogen bond is shown in Fig. 6, which shows that the 5-nitro structure has lower heat of formation values at interplanar angles up to ca 60°. This stabilization effect is supported by calculation of the stabilization energy, which is defined as the difference between the heat of formation of a system that contains molecules of (II) and water molecules separated by 6 Å, and a system that

contains molecules of (II) hydrogen bonded to each water molecule through a single hydrogen bond. Calculations with four water molecules (one for each N—H or carbonyl group) found that the system with four hydrogen bonds has an *intermolecular* hydrogen bond between N(4)—H(4) and water that weakened the $\text{NO}_2 \cdots \text{H}(4) - \text{N}(4)$ intramolecular interaction and the system is less stable than the nonbonded system (E_{stab} of $-2.13 \text{ kJ mol}^{-1}$, where E_{stab} is defined as the difference in the heat of formation values of the systems defined above). In contrast, a system containing only three water molecules, therefore, with no water molecules hydrogen bonded to N(4), was stable, $E_{\text{stab}} = 53.51 \text{ kJ mol}^{-1}$. These calculations suggest that the intramolecular hydrogen bond may be present in solution and in the molecule bonded to the receptor. Since this 5,7-dinitro derivative is the most active compound in the series reported in this article, this persistent intramolecular hydrogen bond suggests that receptor interactions involve only one N—H group.

2.2. Molecular structures

The bond distances in the $-\text{NH}-\text{C}=\text{O}$ fragments show an increased π -delocalization which is correlated with decreases in the hydrogen-bond distances $\text{O} \cdots \text{N}$ or $\text{O} \cdots \text{O}$. This phenomenon has been termed π -cooperativity (Jeffrey & Saenger, 1991) or resonance-assisted hydrogen bonding (RAHB; Gilli, Bertolasi, Ferretti & Gilli, 1993). Following the RAHB formalism, contributions from the polar form can be assessed by comparing a π -delocalization index; which in this case we define as $Q = d_1 - d_2$. Taking $d_1 = 1.47$ and $d_2 = 1.20 \text{ \AA}$ for pure single N—C and double C=O bond lengths and $d_1 = 1.28$ and $d_2 = 1.37 \text{ \AA}$ for pure $\text{N}=\text{C}$ and $\text{C}=\text{O}$

bond lengths (Allen *et al.*, 1987), the maximum value for Q for the pure aminone would be 0.27 \AA and the minimum value for Q for the polar form would be



-0.09 \AA . The fractional contribution from the polar form (λ) can be obtained from the value of Q (Gilli, Bertolasi, Ferretti & Gilli, 1993) by solving the equation: $Q = 0.27(1 - \lambda) + \lambda(-0.09) \text{ \AA}$. As expected, the $-\text{NH}-\text{C}=\text{O}$ fragments that are not hydrogen bonded show a degree of delocalization. Q for O(2) of (I) is 0.151 \AA and for O(3) of (II) is 0.172 \AA ; these values correspond to 33 and 27% contribution from the polar form, respectively. All other carbonyl O atoms in these structures form one or more hydrogen bonds and, in most cases, $\text{C}-\text{H} \cdots \text{O}$ interactions; in all cases the Q values are smaller than the nonbonded examples given above, which suggests resonance-assisted hydrogen bonding. Q values range from 0.150 \AA for an $\text{O} \cdots \text{N}$ contact distance of $2.194(2) \text{ \AA}$ to the two smallest Q values which are found in the structures with the shortest $\text{O} \cdots \text{N}$ contacts: O(2) (III), contact $2.768(2) \text{ \AA}$ and $Q = 0.119 \text{ \AA}$; O(3) (IV), contact $2.829(2) \text{ \AA}$ and $Q = 0.121 \text{ \AA}$. For these short contact distances, the contribution from the polar form has increased to 42 and 41%, respectively. Thus, resonance makes an important contribution to the intricate hydrogen-bonding networks in crystals of QD derivatives.

In both the symmetrically substituted derivatives (I and IV) the bond lengths and angles agree with the molecular symmetry. In (IV) the differences between

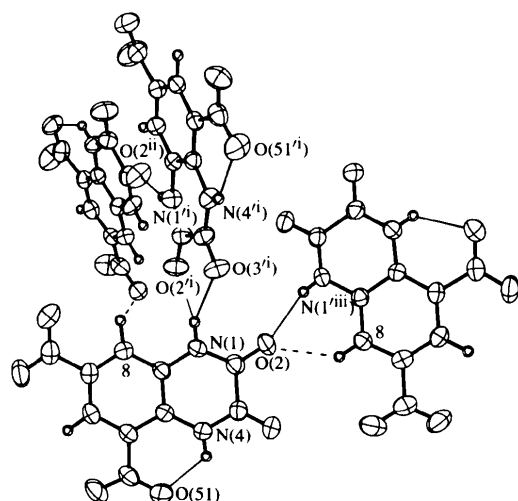


Fig. 5. Hydrogen-bond network for (II). Drawing prepared as in Fig. 1. Symmetry codes: (i) $\frac{1}{2} - x, 1 - y, z - \frac{1}{2}$; (ii) $\frac{1}{2} + x, \frac{1}{2} - y, -z$; (iii) $2 - x, \frac{1}{2} + y, \frac{1}{2} - z$.

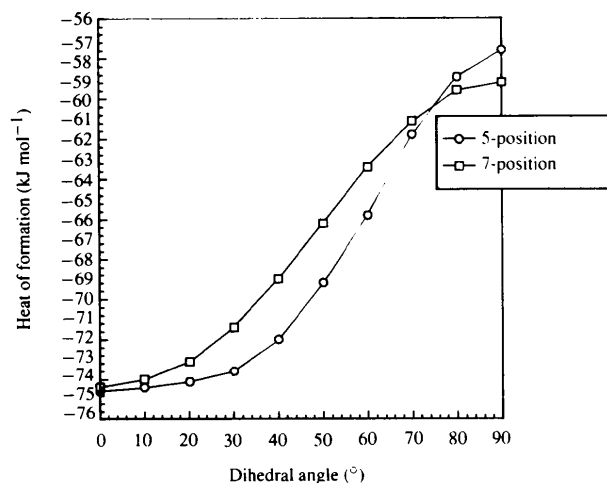


Fig. 6. The heat of formation as a function of the dihedral angle between the molecular plane of (II) and the planes of nitro groups. For every fixed position of one group the geometry of the rest of the molecule was optimized (Stewart, 1990).

Table 5. *The influence of the substituents on the bond-angle pattern in the phenyl ring compared with the results of Domenicano & Murray-Rust (1979)*

(diff)_{ob} is the difference between the actual values of the angle (mean value for II) and the angle for quinoxaline itself (Svensson, 1976); (diff)_{th} is the value obtained from Domenicano & Murray-Rust (1979), assuming additivity in the cases of (II) and (V).

Compound angle	(II)		(III)		(V)	
	(diff) _{ob}	(diff) _{th}	(diff) _{ob}	(diff) _{th}	(diff) _{ob}	(diff) _{th}
C(4A)—C(5)—C(6)	+2.5 (3)	+3.2 (2)	-1.5 (2)	-1.9 (1)	+2.1 (3)	+2.5 (2)
C(5)—C(6)—C(7)	-2.6 (3)	-3.8 (2)	+2.5 (2)	+2.9 (2)	-2.1 (3)	-2.8 (2)
C(6)—C(7)—C(8)	+3.0 (3)	+3.2 (2)	-1.8 (2)	-1.9 (1)	+2.5 (3)	+2.5 (2)
C(7)—C(8)—C(8A)	-1.4 (3)	-1.5 (2)	+0.3 (2)	+0.3 (1)	-2.0 (3)	-1.6 (2)
C(8)—C(8A)—C(4A)	+1.2 (3)	+0.6 (2)	+0.1 (2)	+0.4 (2)	+1.7 (3)	+1.2 (2)
C(8A)—C(4A)—C(5)	-2.7 (3)	-1.5 (2)	+0.4 (2)	+0.3 (1)	-2.1 (3)	-1.6 (2)

symmetrically related parameters are within the $3\sigma_+$ [where $\sigma_+ = (\sigma_1^2 + \sigma_2^2)^{1/2}$] range. In (I), however, the differences are larger, probably due to the lack of a hydrogen bond involving O(2) which produces an asymmetric hydrogen-bonding pattern. This asymmetry is also present to a smaller degree in (V).

In the phenyl rings, the bond length and angle variations are determined mainly by the substituents. For (III), there is only one nitro group and the changes in the bond angles follow the description by Domenicano & Murray-Rust (1979) for substituted benzene derivatives. For the other compounds, the influence of the substituents is more complex. In the symmetrically substituted compounds, (I) and (IV), the neighboring substituents seem to neutralize the effect of one another and the bond-angle patterns resemble closely that of the QD molecule itself (Svensson, 1976). In the 5,7-disubstituted derivatives the influence of the substituents should be additive and even though this additivity is not perfect, a trend is apparent. The differences in the bond angles of (II), (III) and (V) compared with QD itself are listed in Table 5, together with values obtained from the analysis of Domenicano & Murray-Rust (1979). In (II) there are two symmetrically independent molecules in the asymmetric part of the unit cell. The normal probability plot (Abrahams & Keve, 1971; *International Tables for X-ray Crystallography*, 1974) shows that the differences in the geometries of the two molecules are random rather than systematic (correlation coefficient 0.96). The geometries of the nitro groups are similar in the three nitro derivatives and are very close to typical values (Allen *et al.*, 1987). The small, although statistically significant, differences in the N—O bond lengths are probably due to intermolecular interactions.

The QD ring systems of all molecules are approximately planar. The largest deviations from planarity are observed in both molecules of (II), the dihedral angles between the constituent rings are 3.31 (7) and 4.71 (6)° for molecules A and B, respectively. This deviation from planarity is probably due to the formation of an intramolecular N(4)—H(4) ··· O(51) hydrogen bond. As is found for the dinitro derivatives, in the dichloro compounds the 5,7-dichloro derivative shows greater deviation than the 6,7-dichloro derivative.

The orientation of the nitro groups strongly depends on the position of these groups in the aromatic ring. In (I), the nitro groups are in neighboring positions; the crowding causes the nitro groups to be twisted with respect to the molecular plane. The angles between the plane of the nitro group in each of the 6 and 7 positions and the plane of the phenyl ring are 58.87 (5) and 34.69 (7)°, respectively. These values are well inside the range found for similarly substituted nitro compounds, for example, 33.0 (1) and 46.5 (1), 52.2 (2) and 36.0 (2), 17.0 (1) and 66.7 (1), and 41.5 (1) and 41.4 (1)° (Squadrito, Fronczek, Church & Pryor, 1989; Popova *et al.*, 1986; Herbstein & Kapon, 1990). In (III) the nitro group is not crowded and the dihedral angle between the plane of the nitro group and the phenyl ring is equal to 4.9 (2)°. In (II) the 5-nitro group is held approximately coplanar with the quinoxalinedione by an intramolecular hydrogen bond; the twist angles are 6.7 (2)° for molecule A and 4.7 (2)° for molecule B. The orientation of the nitro group at position 7 is probably determined by intermolecular interactions and the twist angles are different for both molecules: 3.5 (2)° for A and 22.9 (3)° for B. The nitro group in molecule A forms a close N(4')—H(4') ··· O(71) hydrogen bond, which may contribute to the coplanarity of the group. In all cases the N atoms of the nitro groups deviate significantly from the mean plane of the phenyl ring; the deviation of the N atom is at least five times greater than the maximum deviation for the atoms that define the plane.

2.3. Graph-set analysis

To obtain insight into the hydrogen-bond patterns of QD derivatives, which may be important to the molecular recognition of the molecule by the EAA receptor, we performed a graph-set analysis of these patterns. Our approach is generally based on the method described by Etter and coworkers (Etter, 1990; Etter, MacDonald & Bernstein, 1990; Bernstein, Etter & MacDonald 1990; Bernstein, 1991). We introduced a graph-set analysis to explore its ability to identify a characteristic molecular interaction pattern that might predict interactions with vastly different partners, including enzyme active sites, molecular surfaces and receptor binding sites. We developed the graph-set notation for compounds reported

Table 6. Graph-set symbols for QD derivatives

Compound	First-order	Graph symbols	
		Second-order	Third-order
QD ^a	$R_2^2(8)C(4)$		
6,7-diCl-QD (IV) ^b	$R_2^2(8)C(4)[R_1^2(5)]$		
6,7-diNO ₂ -QD (I) ^b	$C(8)C(8)[R_1^2(4)]$	$R_3^3(16)[R_1^2(4)]$	
5-Cl-7-NO ₂ -QD ^c	$2R_2^2(8)2R_1^2(5)$	$2C_2^2(8)[2R_1^2(5)]$	
5,7-diNO ₂ -QD (II) ^b	$SSDR_1^2(5)$	$C_2^2(8)[R_1^2(5)]$	
5,7-diCl-QD.DMF (V) ^b	$DR_2^2(8)$		
5-Cl-7-NH ₂ .QD.HCl ^d	$3DR_2^2(8)C(9)$	$C_2^2(9)R_2^2(4)$ $C_2^2(9)C_2^2(6)[R_1^2(5)]^*$	
6,7-diMe-QD.2H ₂ O ^e	$5DR_2^2(8)$		$R_3^3(8)2C_2^2(8)C_3^3(9)$
6,7-diOMe-QD.H ₂ O ^e	$3DC(5)$	$2C_2^2(7)$	$R_3^3(10)$
6-NO ₂ .QD.H ₂ O (III) ^{b,f}	$2DC(5)R_1^2(5)$	$C_2^2(7)C_2^2(6)[R_1^2(5)]$ $R_3^3(8)$	$R_3^3(10)$

References: (a) Svensson (1976); (b) this paper; (c) Grabowski, Stepieñ, Cygler & Wajsman (1977); (d) Stepieñ (1977); (e) Kubicki & Codding (1993); (f) Stepieñ (1981). * This graph set would arise if the H atom is disordered as suggested in the text.

here, in earlier work (Kubicki & Codding, 1993) and those found in the Cambridge Structural Database (Allen *et al.*, 1979). Altogether there are ten structures possessing the QD structural fragment. The graph-set symbols for these QD derivatives are collected in Table 6. C—H...O interactions were not included in this analysis as they provide few unique connections between molecules. It appears that in molecules with strong donors and acceptors, C—H...O interactions contribute to the energy of binding more than they determine specific recognition.

The two structures which crystallize without solvent molecules and have neither additional donors nor acceptors, QD (Svensson, 1976) and (IV), have very similar hydrogen-bonding schemes. These include a centrosymmetric ring, closed by N—H...O hydrogen bonds, $R_2^2(8)$ according to graph-set notation (Etter, MacDonald & Bernstein, 1990), and an infinite chain also made by the N—H...O hydrogen bonds and a glide plane of symmetry $C(4)$. Thus, the first-order graph set can be described as $R_2^2(8)C(4)$. For (IV) the exact symbol should be $R_2^2(8)C(4)[R_1^2(5)]$, in order to describe the three-centered hydrogen bond. Note that one of the bifurcated hydrogen bonds is considerably weaker than the other. As these cases seem to be the simplest, this graph set could serve as the model for investigating the hydrogen-bond schemes for the remaining compounds.

The next three molecules also lack solvent molecules in their structures, however, they are more complicated because of the presence of the nitro groups. For (I), the $C(4)$ motif is present in the crystal structure, but the other N—H group makes hydrogen bonds with the nitro groups, creating a motif $C(8)[R_1^2(4)]$. The second-order graph set shows a three-molecule ring: $R_3^3(16)[R_1^2(4)]$. In the structure of 5-chloro-7-nitro-QD (Grabowski, Stepieñ, Cygler & Wajsman, 1977), there are two symmetry-independent molecules in the asymmetric part of the unit cell. The first-order graph set includes two centrosymmetric hydrogen-bonded dimers, $2R_2^2(8)$, and two $R_1^2(5)$ rings made by the three-centered hydrogen

bonds connecting the two symmetrically independent molecules. The second-order graph set describes the $-ABAB-$ chains of the molecules, $2C_2^2(8)[2R_1^2(5)]$.

The case of (II) is different from all the other QD derivatives, because it crystallizes in a noncentrosymmetric space group, which does not allow the formation of the centrosymmetric dimer and it has an intramolecular hydrogen bond. The first-order graph set includes two intramolecular hydrogen bonds, $2S$, and one noncyclic dimer, D , describing the two-centered hydrogen bond plus a ring $R_1^2(4)$ describing the three-centered hydrogen bond which connects the symmetry-independent molecules. The second-order graph set describes the $-ABAB-$ chains: $C_2^2(8)[R_1^2(4)]$. The weak N(4)—H(4)...O(NO₂) hydrogen bonds create two additional noncyclic dimers.

The remaining five derivatives contain solvent molecules in the crystal structures. The first-order graph set for (V) is $DR_2^2(8)$, where D describes the noncyclic hydrogen bond between the QD and DMF molecules. There is, in addition, a second-order ring, $R_4^4(14)$, closed by weak C—H...O interactions. In the structure of 5-chloro-7-amino-QD hydrochloride (Stepieñ, 1977) there is an $R_2^2(8)$ ring, a $C(9)$ chain created by one of the amino H atoms and three noncyclic dimers describing the hydrogen bonds with the hydrochloride molecule. The second-order graphs include a $C_2^2(9)$ chain of molecules connected through the hydrochloride molecules and an unusual $R_2^2(4)$ ring, created by the N(amino)—H...Cl—H...H(amino) hydrogen-bond system.

The last three compounds contain water molecules which complicate the graph sets, because the water molecules can (and actually do) make their own hydrogen-bond systems. In 6,7-dimethyl-QD dihydrate (Kubicki & Codding, 1993) four water molecules create a fourth-order ring, $R_4^4(8)$. The first-order set includes one centrosymmetric ring, $R_2^2(8)$, and five noncyclic dimers, $5D$, for the hydrogen bonds between different molecules. The second-order graphs have only acyclic sets. For the third-order graphs new features appear: a $R_3^3(8)$ ring,

closed between the H(4) and O(3) atoms of the same molecule by two water molecules, two $C_3^3(8)$ chains and one $C_3^3(9)$ chain, created by N(4)—H(4) and two water molecules. For 6,7-dimethoxy-QD hydrate (Kubicki & Coddling, 1993) the first-order set contains a $C(5)$ chain, created by one of the N—H groups, and three noncyclic dimers, $3D$. The second-order set includes, besides the noncyclic dimers, two $C_2^2(7)$ chains created by sequences of one QD and water molecules. The third-order graph shows the first ring, $R_3^3(10)$, closed by two QD and one water molecule. Lastly, in the structure of (III) there is a $C(5)$ chain, the three-centered ring $R_1^2(5)$ and two noncyclic dimers in the first-order graph set. In the second-order graph, there are two chains: $C_2^2(7)$ and $C_2^2(6)[R_1^2(5)]$, and a ring $R_4^2(8)$, created by two water molecules and two O(3) atoms. For the third-order graph there is a ring, $R_3^3(10)$, closed by two QD and one water molecules.

We have also examined a number of structures which contain the QD skeleton and have fewer hydrogen-bonding groups. Our goal is to identify the minimum structural features required to achieve the common hydrogen-bond pattern, as exemplified by similar graph sets. First, we examined the graph sets for compounds with one of the N—H groups blocked. The hydrogen-bond networks are quite similar for the three independent molecules with an 1,8-ethano bridge (Kubicki, Kindopp, Capparelli & Coddling, 1992). For the 6-bromo derivative, there is a simple $C(4)[R_1^2(5)]$ chain; since this crystal has two molecules per asymmetric part of the unit cell, there is second-order chain $C_2^2(9)[R_1^2(5)]$. For the 6-methyl hydrate, there are second-order chains, $C_2^2(7)$ and $C_2^2(6)[R_1^2(5)]$, created by the QD and water molecules, and a $R_4^2(8)$ ring closed by two water molecules and two O(3) atoms. Two other compounds, 1-methyl-4-hydro-5-chloro-6-nitro-2,3-quinoxalinedione and 1-methyl-4-hydroxyl-6-nitro-2,3-quinoxalinedione hydrate (McFarlane, Smith, Ferguson & Kaitner, 1989), create hydrogen-bonded rings: one first-order $R_2^2(8)$ for the former and two second-order $R_4^2(14)[2R_1^2(5)]$ — $R_4^2(20)[2R_1^2(4)]$ for the latter. In the latter the rings are formed by two water and two compound molecules, the second being created by strong three-centered hydrogen bonds with both O atoms of the nitro group.

For the compounds with only one donor and one acceptor, rings appear as the most common hydrogen-bond motifs. The only exception is 1-hydro-2-quinoxalinedione (Stepień, Grabowski, Cygler & Wajzman, 1976; Padmaja, Ramakumar & Viswamitra, 1987), which crystallizes in a noncentrosymmetric space group and has a $C(4)$ chain motif. For all other cases in which the donor and the acceptor are available for intermolecular interactions, there are $R_2^2(8)$ rings. In two cases the two independent molecules in the asymmetric part of the noncentrosymmetric unit cell close a $R_2^2(8)$ ring: meloscandone (Rodier, Mauguen, Hachem-Mehri & Plat, 1978) and 3-[L-*threo*-2,3,4-triacetoxy-1-(phenyl-

hydrazono)]-quinoxalin-2(1*H*)-one (Amer *et al.*, 1990). This observation suggests that there is a strong tendency towards the formation of a (at least pseudo-) centrosymmetric ring. For the latter compound, the evidence for a noncentrosymmetric structure is weak and the graph set may reflect the true crystal symmetry: the coordinates of the atoms are very close to centrosymmetric, the water molecule lies almost exactly on what would be the center of symmetry, the R factor is high, the fraction of observed reflections is low and the residual electron density is relatively high.

3. Conclusions

Hydrogen bonding is an important part of molecular recognition processes. Our basic assumption is that any topological preferences observed at the binding site of a receptor will also be found in the crystal structures of compounds with a high affinity for that site. The graph-set analysis of the hydrogen-bond networks in the known structures of the QD derivatives, as listed in Table 6, show that there is a strong tendency to form both hydrogen-bonded rings and chains. This tendency is sometimes obscured by the presence of more than one molecule per asymmetric part of the unit cell or by the solvent molecules in the crystal structure. In these cases, similar graphs appear at a higher level. Unfortunately, the rules for assigning the graph-set notation, while providing exactness in the description of the true topology of the crystal, obscure the general similarities of the hydrogen bonding that is characteristic of the molecule of interest. Nevertheless, a basic ring and chain motif, similar to the $R_2^2(8)C(4)$ graph set found for QD itself, is present in the majority of the analyzed compounds. If one of these motifs appears at a higher level, both the dimensions and the number of donors and acceptors are multiplied (generally, by the order of the graph). An example is found in Fig. 2, which presents the hydrogen bonding of (III), the graph set at the third order being $R_3^3(10)$; however, for the QD molecule this actually represents the same type of hydrogen-bond interaction that is found in an R_2^2 ring when solvent is not present, see Fig. 3 for (IV).

A few exceptions are found to the generalization of a ring and chain; however, these are relatively easy to explain. For the 5,7-dinitro-QD (II) compound the presence of an intramolecular hydrogen bond dramatically changes the hydrogen-bond properties of the compound so that it can be regarded as a one donor—two acceptor molecule and be expected to have a graph set typical of that type of QD—either a chain or a ring are formed, rarely both. The relatively bulky DMF molecule in the crystal structure of 5,7-dichloro-QD (V) and the hydrogen-bond properties of the solvent (good acceptor, poor donor) also change the possibilities of creation of hydrogen bonds by such a complex. In fact, the DMF molecule acts as a terminator of a hydrogen bond; the

complex of QD-DMF might also be regarded as a one donor–two acceptor system.

In one case there were no unusual features in the structure (either intramolecular hydrogen bonds or poorly bonding solvents) that could explain the exception. In the structure of 5-chloro-7-amino-QD hydrochloride (Stepień, 1977) unusual features were observed in the graph set and a chain connecting the N—H···O atoms was not observed; the source of the difference was the poorly defined H atom of the hydrochloride. Based on separations between donor and acceptor atoms, rather than the H-atom position, we found a potential bifurcated hydrogen bond which would require that the H atom of the solvent be disordered. The bond would involve Cl(solvent)···O(2) and O(3) at $(-\frac{1}{2} + x, \frac{1}{2} - y, 1 - z)$. The Cl···O distances are 3.123(3) Å for O(2) and 3.084(4) Å for O(3). If this is correct, there will be an additional second-order motif, $C_2^2(6)[R_1^2(5)]$, and we have added this possibility to Table 6. Thus, our effort to define a distinctive molecular pattern using graph-set analysis found instead that the analysis has predictive power and we suggest that the hydrogen bonding in this structure is different from that presented in the original paper.

To establish the minimum number of hydrogen-bond interactions required for the common hydrogen-bonding motif of QD derivatives, we examined molecules related to QD that have fewer hydrogen-bonding groups. For compounds with one amino group blocked which are, thus, one donor–two acceptor systems, there is an almost equal probability of formation of either a ring or a chain (as noted in the two exceptions mentioned above). For a one donor–one acceptor system the formation of a ring is highly predominant and the chain motif is rare; thus, the diminution of the number of hydrogen-bonding groups diminishes the choices of interactions with the receptor. The minimum fragment that would permit the maximum choice and maximum number of interactions between the QD molecule and the receptor is likely to be preferred in receptor recognition. Therefore, we propose that the required features are one hydrogen-bond donor and two acceptors; this proposal is consistent with the structure–activity data on QD derivatives (Pullan, 1991).

The graph-set approach enabled us to describe the global features of the hydrogen-bond networks in an elegant way. Application over a broad class of compounds with the aim of finding a distinctive molecular interaction motif showed that this method has the potential for finding missed structural features. However, since we are mainly interested in the hydrogen-bond properties of the QD molecules themselves, we find that the rigorous application of graph-set notation, which provides a precise description of the crystal topology, obscures the general similarities of the hydrogen-bonding pattern. It may be necessary to develop another method for extracting molecular properties from the graph set, while recognizing the power of

the graph set to describe all the possible combinations of hydrogen-bonding patterns that a molecule can adopt.

This work was supported by the Medical Research Council of Canada (grant to PWC).

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