organic compounds

Two *N,N*-dimethylbiguanidium salts displaying double hydrogen bonds to the counter-ions

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The crystal structures of *N,N*-dimethylbiguanidium oxalate monohydrate, $C_4H_{13}N_5^{2+} \cdot C_2O_4^{2-} \cdot H_2O$, (I), and *N,N*-dimethylbiguanidium sulfate monohydrate, $C_4H_{13}N_5^{2+} \cdot SO_4^{2-} \cdot H_2O$, (II), show that both compounds contain the same *N,N*-dimethylbiguanidium dication. In (I), two independent oxalate ions lie about inversion centres. Strong double hydrogen bonds, with $D \cdots A$ distances of 2.658 (2) and 2.830 (3) Å in (I), and 2.722 (3) and 2.815 (3) Å in (II), are present between N atoms of the *N,N*-dimethylbiguanidium moieties and either the carboxylate group of the oxalate anion or the sulfate anion.

Comment

An N-substituted derivative of biguanide, *viz.* metformin (*N,N*-dimethylbiguanide), is a powerful oral antihyperglycaemic drug that has been used in many countries for over 40 years for treating diabetic patients with non-insulin-dependent diabetes mellitus. However, the mechanism of action of this drug is still unknown. Because this compound contains a biguanidium group, it can form complexes with many metal ions (Ray, 1961; Zhu *et al.*, 2002, 2002*a,b*; Lu, Yang *et al.*, 2004). Recently, we found that *N,N*-dimethylbiguanide loses its ability to lower blood glucose levels when forming a monodentate complex with Zn^{2+} ions, but retains this ability when forming bidentate complexes with Cu^{2+} and Ni^{2+} ions (Zhu *et al.*, 2004). On the other hand, guanidium may play an important role in recognizing anions, such as carboxylates, phosphates, sulfates and nitrates, in biological systems (Baggio *et al.*, 1997; Liu *et al.*, 2001; Lu *et al.*, 2001; Best *et al.*, 2003). It has been proven that a strong interaction between the guanidium groups and anions through charge pairing and hydrogen bonding facilitates the recognition of small target anions by receptors containing guanidinium groups in

competitive solvent systems (Best *et al.*, 2003). We elucidate here the possible mechanism of *N,N*-dimethylbiguanide interacting with target molecules by reporting the crystal structures of *N,N*-dimethylbiguanidium oxalate monohydrate, (I), and *N,N*-dimethylbiguanidium sulfate monohydrate, (II).
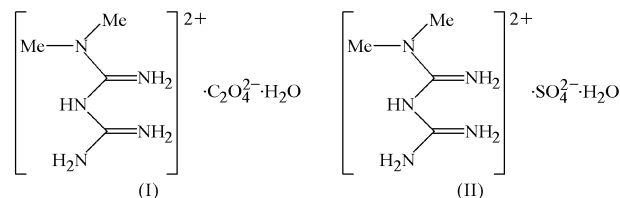
Some features of the molecular geometries of (I) and (II) are listed in Tables 1 and 3. The molecular conformation is illustrated in Figs. 1 and 2. Compound (I) contains one *N,N*-dimethylbiguanidium dication, one oxalate anion and one water molecule. Compound (II) consists of one *N,N*-dimethylbiguanidium dication, one sulfate anion and one water molecule. Both compounds thus contain the same *N,N*-dimethylbiguanidium dication. The C—N bonds of the biguanidium moiety range from 1.302 (3) to 1.374 (3) Å in (I) and 1.308 (4) to 1.383 (4) Å in (II); this situation differs from that in *N,N*-dimethylbiguanidium nitrate, in which the C—N bonds are more uniform [1.324 (3)–1.343 (3) Å; Zhu *et al.*, 2003]. The dihedral angles between the two guanidine group planes are 52.8 (1) and 56.1 (1)° in (I) and (II), respectively. Therefore, the anions slightly influence the structure of *N,N*-dimethylbiguanide.

The hydrogen-bonding geometries in (I) and (II) are listed in Tables 2 and 4 and illustrated in Figs. 3 and 4. A number of intra- and intermolecular hydrogen bonds stabilize the crystal structure of each compound. These hydrogen bonds are formed mainly between the biguanidium groups and the oxalate or sulfate anions, between the biguanidium groups and the water molecules, as well as between the carboxylate or sulfate anions and water molecules. Strong double hydrogen bonds are formed between either the carboxylate groups of the oxalate anion or the sulfate groups and atoms N3 and N5
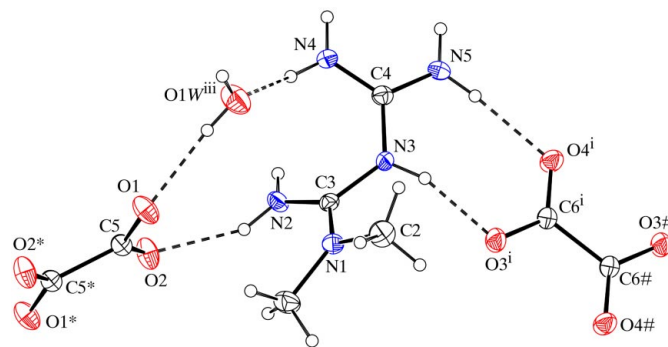

Figure 1
The structure of (I), with displacement ellipsoids drawn at the 30% probability level for non-H atoms. [Symmetry codes: (*) $2 - x, 2 - y, 2 - z$; (#) $-x, \frac{1}{2} + y, \frac{1}{2} - z$; symmetry codes (i) and (iii) are as defined in Table 2.]

of the biguanidium groups of the cation. The $D\cdots A$ distances are 2.658 (2) and 2.830 (3) Å in (I), and 2.815 (3) Å in (II), giving rise to an elongated hexagonal configuration. Double hydrogen bonds are also found in N,N-dimethylbiguanidium nitrate at the corresponding N3- and N5-atom sites, but these bonds are formed between a pair of N,N-dimethylbiguanidium cations, not between the N,N-dimethylbiguanidium cations and the nitrate anions (Zhu *et al.*, 2003). Therefore, the N,N-dimethylbiguanidium cation exhibits a common characteristic that the N3- and N5-atom sites take part in the formation of double hydrogen bonds, in contrast to the double hydrogen bonds formed in biguanidium nitrate, in which double hydrogen bonds are formed between nitrate anions and atoms N1 and N2 or N4 and N5 of the biguanidium cation (Lu, Zhu & Yang, 2004). Because N,N-dimethylbiguanide loses its ability to lower blood glucose levels when complexing with the Zn^{2+} ion at the N3-atom site (perhaps interfering with the formation of double hydrogen
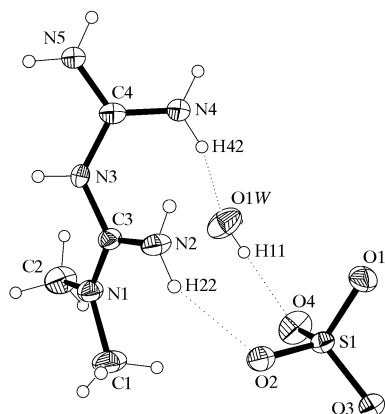

Figure 2
The structure of (II), with displacement ellipsoids drawn at the 40% probability level.
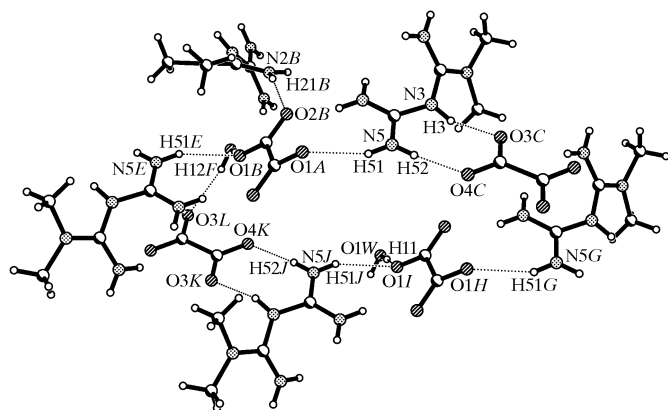

Figure 3
The double hydrogen bonds between atoms N3 and N5 of the biguanidium groups and the carboxylate groups of the oxalate anion in (I). [Symmetry codes: (A) $x, \frac{3}{2} - y, -\frac{1}{2} + z$; (B) $2 - x, y - \frac{1}{2}, \frac{3}{2} - z$; (C) $x, \frac{3}{2} - y, -\frac{1}{2} + z$; (E) $2 - x, 1 - y, 1 - z$; (G) $-1 + x, y, z$; (H) $-1 + x, \frac{3}{2} - y, -\frac{1}{2} + z$; (I) $1 - x, -\frac{1}{2} + y, \frac{3}{2} - z$; (J) $1 - x, 1 - y, 1 - z$; (K) $1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$; (L) $1 + x, \frac{1}{2} - y, \frac{1}{2} + z$.]
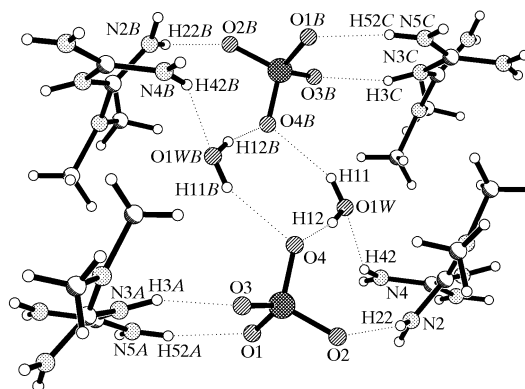

Figure 4
The double hydrogen bonds between atoms N3 and N5 of the biguanidium groups and the sulfate anions in (II). [Symmetry codes: (A) $x - 1, y - 1, z$; (B) $1 - x, 1 - y, 1 - z$; (C) $2 - x, 2 - y, 1 - z$.]

bonds), and yet retains this ability when forming bidentate complexes with Cu^{2+} and Ni^{2+} ions at the N2 and N4 sites, we speculate that this double hydrogen bond between N,N-dimethylbiguanide and its target molecules plays an important role in the interaction with target molecules in biological systems.

Experimental

All chemicals (of reagent grade) were available commercially from the Beijing Chemical Reagents Company, People's Republic of China, and were used without further purification. N,N-Dimethyl-biguanide was obtained from a 1:1 molar ratio of N,N-dimethyl-biguanide hydrochloride and NaOH in 2-propanol. The suspension was stirred for an hour at 313 K and then filtered. The filtrate was evaporated and a white solid, without Cl^- content (checked by 0.1 *M* $AgNO_3$ solution), was collected. Compounds (I) and (II) were prepared by dissolving N,N-dimethylbiguanide (10.0 mmol) in water (5 ml), adding either oxalic or sulfuric acid and adjusting the pH to 4. Crystals of both compounds were obtained from their respective solutions after several weeks, by slow evaporation of the aqueous solvent at room temperature.

Compound (I)

Crystal data

$C_4H_{13}N_5{}^{2+}\cdot C_2O_4{}^{2-}\cdot H_2O$	Mo $K\alpha$ radiation
$M_r = 237.23$	Cell parameters from 1102
Monoclinic, $P2_1/c$	reflections
$a = 6.775$ (2) Å	$\theta = 2.3–22.0°$
$b = 10.762$ (3) Å	$\mu = 0.13$ mm^{-1}
$c = 14.731$ (4) Å	$T = 298$ (2) K
$\beta = 92.561$ (4)°	Block, colorless
$V = 1073.1$ (5) Å^3	$0.40 \times 0.18 \times 0.12$ mm
$Z = 4$	
$D_x = 1.468$ Mg m^{-3}	

Data collection

Bruker SMART 1K CCD area-detector diffractometer	1885 independent reflections
	1295 reflections with $I > 2\sigma(I)$
ω scans	$R_{int} = 0.059$
Absorption correction: multi-scan	$\theta_{max} = 25.0°$
(*SADABS*; Sheldrick, 2000)	$h = -8 \rightarrow 7$
$T_{min} = 0.950$, $T_{max} = 0.985$	$k = -12 \rightarrow 6$
4303 measured reflections	$l = -17 \rightarrow 17$

organic compounds

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0368P)^2]$
$R[F^2 > 2\sigma(F^2)] = 0.046$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.102$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.02$	$\Delta\rho_{max} = 0.24$ e Å^{-3}
1885 reflections	$\Delta\rho_{min} = -0.23$ e Å^{-3}
155 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °) for (I).

C3—N2	1.312 (3)	C4—N4	1.302 (3)
C3—N1	1.323 (3)	C4—N5	1.312 (3)
C3—N3	1.374 (3)	C4—N3	1.361 (3)
N2—C3—N1	123.7 (2)	N4—C4—N3	121.4 (2)
N2—C3—N3	119.5 (2)	N5—C4—N3	116.6 (2)
N1—C3—N3	116.7 (2)	C4—N3—C3	125.4 (2)
N4—C4—N5	122.0 (2)		
N4—C4—N3—C3	20.3 (3)	N2—C3—N3—C4	41.0 (3)
N5—C4—N3—C3	−161.9 (2)	N1—C3—N3—C4	−143.1 (2)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N2—H21$\cdots$O2	0.86	1.97	2.774 (2)	155
N3—H3$\cdots$O3^i	0.86	1.85	2.658 (2)	157
N4—H41$\cdots$O1^{ii}	0.86	2.10	2.873 (2)	149
N4—H42$\cdots$O1W^{iii}	0.86	2.18	2.926 (3)	145
N5—H51$\cdots$O1^{ii}	0.86	2.26	2.986 (3)	143
N5—H52$\cdots$O4^i	0.86	1.97	2.830 (3)	175
O1W—H12$\cdots$O3^{iv}	0.82	2.13	2.934 (3)	169
O1W—H11$\cdots$O1^v	0.82	1.97	2.786 (2)	173
N2—H22$\cdots$O4^{vi}	0.86	2.20	2.874 (2)	135

Symmetry codes: (i) $x, \frac{3}{2} - y, \frac{1}{2} + z$; (ii) $x, \frac{3}{2} - y, z - \frac{1}{2}$; (iii) $1 - x, \frac{1}{2} + y, \frac{3}{2} - z$; (iv) $x, \frac{1}{2} - y, \frac{1}{2} + z$; (v) $1 - x, y - \frac{1}{2}, \frac{3}{2} - z$; (vi) $1 - x, \frac{1}{2} + y, \frac{3}{2} - z$.

Compound (II)

Crystal data

$C_4H_{13}N_5^{2+}\cdot SO_4^{2-}\cdot H_2O$	$D_x = 1.512$ Mg m^{-3}
$M_r = 245.27$	Mo $K\alpha$ radiation
Triclinic, $P\bar{1}$	Cell parameters from 1531
$a = 7.056$ (3) Å	reflections
$b = 8.862$ (4) Å	$\theta = 2.5–26.9°$
$c = 9.462$ (4) Å	$\mu = 0.32$ mm^{-1}
$\alpha = 99.830$ (6)°	$T = 293$ (2) K
$\beta = 96.020$ (7)°	Block, colorless
$\gamma = 110.099$ (7)°	$0.32 \times 0.15 \times 0.15$ mm
$V = 538.8$ (4) Å^3	
$Z = 2$	

Data collection

Bruker SMART 1K CCD area-detector diffractometer	1508 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.040$
ω scans	$\theta_{max} = 25.0°$
Absorption correction: multi-scan	$h = -8 \rightarrow 6$
($SADABS$; Sheldrick, 2000)	$k = -10 \rightarrow 10$
$T_{min} = 0.903$, $T_{max} = 0.954$	$l = -11 \rightarrow 10$
2516 measured reflections	
1741 independent reflections	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0993P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.044$	$+ 0.1217P]$
$wR(F^2) = 0.162$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.18$	$(\Delta/\sigma)_{max} < 0.001$
1739 reflections	$\Delta\rho_{max} = 0.37$ e Å^{-3}
139 parameters	$\Delta\rho_{min} = -0.36$ e Å^{-3}
H-atom parameters constrained	

Table 3
Selected geometric parameters (Å, °) for (II).

C3—N1	1.308 (4)	C4—N4	1.308 (4)
C3—N2	1.314 (4)	C4—N5	1.310 (4)
C3—N3	1.383 (4)	C4—N3	1.370 (4)
N1—C3—N2	123.1 (3)	N4—C4—N3	120.4 (3)
N1—C3—N3	117.8 (3)	N5—C4—N3	117.2 (3)
N2—C3—N3	118.9 (3)	C4—N3—C3	126.1 (2)
N4—C4—N5	122.4 (3)		
N4—C4—N3—C3	26.4 (4)	N1—C3—N3—C4	−144.4 (3)
N5—C4—N3—C3	−157.0 (3)	N2—C3—N3—C4	39.4 (4)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N2—H22$\cdots$O2	0.86	2.06	2.854 (3)	153
N2—H21$\cdots$O1^{vii}	0.86	2.01	2.784 (3)	150
N3—H3$\cdots$O3^{viii}	0.86	1.90	2.722 (3)	159
N4—H41$\cdots$O3^{ix}	0.86	2.05	2.895 (3)	167
N4—H42$\cdots$O1W	0.86	2.07	2.825 (4)	146
N5—H51$\cdots$O2^{ix}	0.86	1.96	2.810 (3)	172
N5—H52$\cdots$O1^{viii}	0.86	1.97	2.815 (3)	169
O1W—H11$\cdots$O4^x	0.82	2.05	2.799 (4)	152
O1W—H12$\cdots$O4	0.82	1.95	2.755 (4)	168

Symmetry codes: (vii) $1 - x, 1 - y, -z$; (viii) $1 + x, 1 + y, z$; (ix) $x, 1 + y, z$; (x) $1 - x, 1 - y, 1 - z$.

In both (I) and (II), H atoms attached to C and N atoms were placed in idealized positions (Csp^3—H = 0.96 Å and Nsp^2—H = 0.86 Å) and constrained to ride on their parent atoms, with U_{iso}(H) values of $1.5U_{eq}$(C) or $1.2U_{eq}$(N). H atoms attached to O atoms were located from difference Fourier maps and allowed for as riding atoms with O—H distances of 0.82 Å allowing common U_{iso}(H) values to refine.

For both compounds, data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1999); software used to prepare material for publication: *SHELXTL/PC*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1242). Services for accessing these data are described at the back of the journal.

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