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The Crystal Structure of Metoclopramide

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The crystal structure of metoclopramide, $C_{14}H_{22}ClN_3O_2$, has been determined by X-ray diffraction techniques using diffractometer data obtained by the ω–2θ scan technique with Mo Kα radiation from a crystal with space group symmetry P$\bar{1}$ and unit cell parameters $a = 7.500(1)$, $b = 8.707(2)$, $c = 13.292(2)$ Å; $\alpha = 101.70(2)$, $\beta = 81.20(2)$, and $\gamma = 114.90(1)°$. The sructure was solved by direct methods and refined by full–matrix least–squares to a final R = 0.055 for the 1524 observed reflections. The bent overall–conformation of the molecule seems to be determined mainly by the bifurcated intramolecular hydrogen bond from the amide nitrogen atom to the methoxy oxygen and the amine nitrogen atoms. The crystal packing consists of the hydrogen bonds, π–π interaction and hydrophobic interaction.

Introduction

Metoclopramide, N–(diethylaminoethyl)–2–methoxy–4–amino–5–chlorobenzamide, is a widely used antiemetic agent which stimulates orthograde peristalsis and thus suppresses the reflux of the bile.[1] The metoclopramide molecule has many rotatable single bonds especially in the trialkylamine portion of the molecule. The crystal structure analysis of the hydrochloride salt of metoclopramide has been recently published.[2] Comparison of the crystal structures in different protonation state and crystal environment will provide an opportunity to determine whether there is any salient feature in the stable overall conformation of this apparently flexible molecule and, if so, what are the major factors for assuming that conformation. The structural study is desirable to establish the structure–activity relationship and we report the results of the crystal structure analysis of the unprotonated metoclopramide.

Experimental

Metoclopramide was crystallized by slow evaporation from an aqueous methanol solution in the form of transparent rectangles at room temperature. The crystals were triclinic as determined from oscillation and Weissenberg photographs. The space group which was initially assumed to be P$\bar{1}$ was confirmed later in the crystal structure determination and refinement. The unit cell parameters were determined by a least–squares fit of the 2θ angles for 25 reflections measured with Mo Kα radiation on a Rigaku AFC diffractometer.[3] All of the pertinent crystal data are summarized in Table 1. The intensity data were collected with graphite–monochromated Mo Kα radiation by the ω–2θ scan technique over a scan range of $(1.2+0.5 \tan \theta)°$ in ω at a scan rate of 4°/min and a 10–s background count at each end of the scan range.

Three standard reflections were monitored after each 50 data reflections and showed no appreciable variations in

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TABLE 1: Crystal Data for Metoclopramide

$C_{14}H_{22}ClN_3O_2$	M. W. 299.81

triclinic; space group P$\bar{1}$; Z=2

a=7.500(1) Å	α=101.70(2)°
b=8.707(2)	β=81.20(2)
c=13.292(2)	γ=114.90(1)
V=768.72 Å³	F(000)=320

D_m=1.19 g cm⁻³ by flotation in benzene-chloroform
D_c=1.198 g cm⁻³
μ(Mo Kα)=2.11 mm⁻¹
crystal size; 0.5×0.3×0.2 mm

intensities throughout the entire data collection. The intensity data were converted to relative structure factor amplitudes after correction for Lorentz and polarization effects appropriate for graphite-monochromated radiation as the intensity data were collected.[3] Of the 2682 independent reflections measured within the range of $2\theta \leq 55.0°$, 1524 were

considered observed, as defined by $|F| \geq 6\sigma(F)$. No correction for the absorption and the extinction effects was made.

Structure Determination and Refinement

The observed structure amplitudes were normalized to E values by means of a Debye plot using the program MULTAN[4]. The statistical distribution of E values was indicative of the space group P$\bar{1}$. Numerous attempts to solve the structure either by the direct methods using the program MULTAN or by the heavy atom methods resulted in failure. The structure was finally solved using the centrosymmetric direct methods program in SHELX 76 system.[5] From the E map of the set with the second highest reliability index it was possible to identify 15 nonhydrogen atoms among the 20 atoms in the molecule. One cycle of isotropic full–matrix least–squares refinement reduced the conventional R value $(R=\Sigma||Fo|-k|Fc||/\Sigma|Fo|$ where k is a single scale factor) from

TABLE 2: Fractional Coordinates and Temperature Factors for Metoclopramide

A. Nonhydrogen Atoms[a]

atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl	3188(3)	283(2)	3066(1)	65(1)	55(1)	31(1)	2(1)	−10(1)	23(1)
O(1)	2105(7)	−895(5)	−1331(3)	61(3)	33(3)	27(2)	−2(2)	−10(2)	22(2)
O(2)	2618(7)	3722(5)	497(3)	62(3)	30(3)	43(3)	−4(2)	−7(2)	21(2)
N(1)	2773(10)	−2923(8)	1629(5)	65(5)	38(4)	50(4)	9(3)	−5(3)	26(4)
N(2)	2489(9)	2346(7)	−1114(4)	50(4)	30(3)	39(3)	1(3)	−2(3)	22(3)
N(3)	3999(9)	2987(7)	−3306(4)	57(4)	34(3)	27(3)	7(2)	−1(3)	13(3)
C(1)	2521(9)	925(8)	274(5)	27(4)	31(3)	37(4)	−2(3)	−4(3)	12(3)
C(2)	2363(9)	−651(8)	−322(5)	25(4)	35(4)	31(3)	−2(3)	−2(3)	8(3)
C(3)	2438(10)	−1912(8)	151(5)	42(4)	27(4)	31(3)	3(3)	−1(3)	14(3)
C(4)	2733(9)	−1660(8)	1181(5)	32(4)	39(4)	41(4)	3(3)	−5(3)	15(3)
C(5)	2852(9)	−109(9)	1761(4)	36(4)	47(4)	22(3)	−1(3)	−4(3)	15(3)
C(6)	2764(10)	1147(8)	1306(5)	36(4)	27(3)	36(4)	1(3)	0(3)	11(3)
C(7)	1737(13)	−2546(9)	−1924(6)	61(5)	32(4)	40(4)	−7(3)	−7(4)	19(4)
C(8)	2544(9)	2442(8)	−118(4)	26(4)	35(4)	26(3)	7(3)	2(3)	11(3)
C(9)	2580(11)	3779(8)	−1559(5)	55(5)	33(4)	29(3)	9(3)	2(3)	23(4)
C(10)	2313(12)	3231(10)	−2702(5)	59(5)	40(4)	40(4)	7(3)	−16(3)	18(4)
C(11)	5506(14)	4622(11)	−3506(7)	73(6)	55(5)	50(5)	12(4)	8(4)	15(4)
C(12)	7455(18)	4604(17)	−3973(9)	79(8)	102(9)	79(7)	41(6)	−9(6)	3(7)
C(13)	3368(14)	1836(10)	−4268(6)	81(6)	48(5)	33(4)	−1(3)	−9(4)	21(4)
C(14)	2239(15)	0(11)	−4113(7)	78(7)	50(5)	55(5)	−11(4)	−16(5)	22(5)

B. Hydrogen Atom[b]

atom	x	y	z	U	atom	x	y	z	U
H(N11)	273(10)	−370(9)	145(5)	40	H(C102)	100(10)	214(8)	−285(5)	45
H(N12)	384(10)	−251(8)	205(5)	40	H(C111)	545(11)	535(9)	−294(6)	57
H(N2)	256(10)	155(9)	−156(5)	45	H(C112)	490(10)	513(9)	−381(5)	57
H(C3)	220(9)	−292(8)	−7(5)	37	H(C121)	813(13)	419(11)	−358(7)	74
H(C6)	296(9)	220(8)	154(5)	45	H(C122)	714(12)	415(11)	−459(7)	74
H(C71)	41(10)	−351(8)	−155(5)	49	H(C123)	847(13)	584(11)	−404(6)	74
H(C72)	121(10)	−258(8)	−262(5)	49	H(C131)	268(10)	218(8)	−460(5)	48
H(C73)	294(10)	−274(9)	−198(5)	49	H(C132)	457(10)	193(9)	−472(5)	48
H(C91)	404(9)	493(8)	−148(5)	38	H(C141)	188(11)	−75(9)	−465(6)	56
H(C92)	156(9)	409(8)	−138(5)	38	H(C142)	313(11)	−22(9)	−381(6)	56
H(C101)	200(9)	407(8)	−300(5)	45	H(C143)	81(11)	−23(8)	−378(5)	56

[a] Positional parameters ×10⁴; thermal parameters ×10³; the expression used for the anisotropic temperature factor is $\exp(-\{2\pi^2(h^2a^{*2}U_{11}+\cdots2hka^*b^*U_{12})\})$. Estimated standard deviation in parentheses is for the least significant figure.

[b] All parameters ×10³; the expression used for the isotropic temperature factor is $\exp(-[(8\pi^2U)\sin^2\theta/\lambda^2])$.
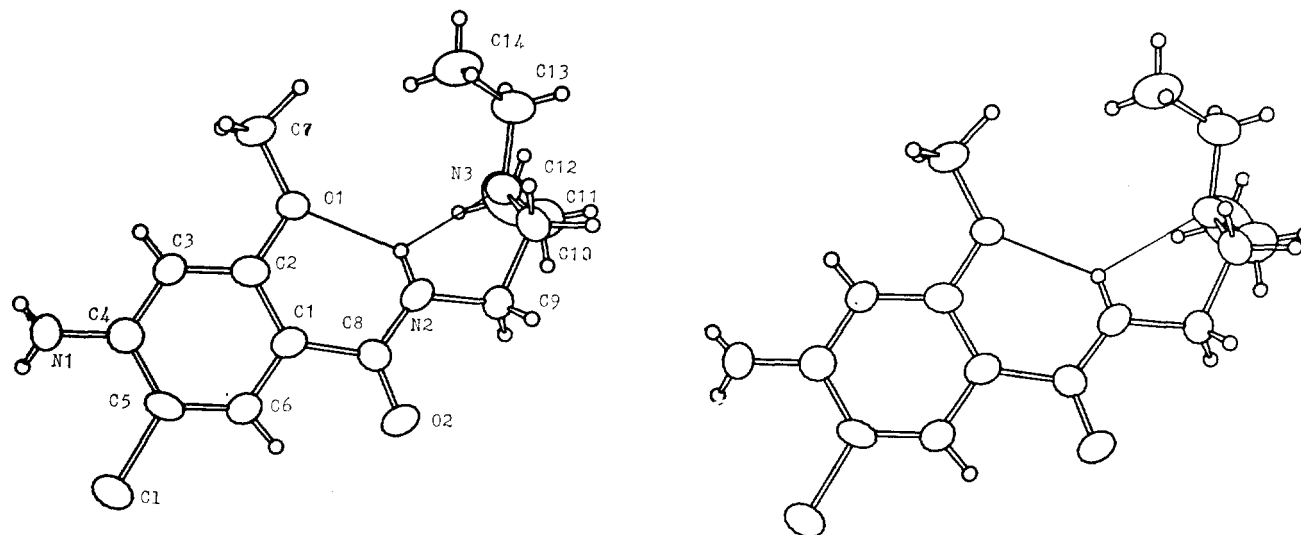
Figure 1. Stereoscopic ORTEP[7] drawing of the metoclopramide molecule. The thermal ellipsoid boundaries are at the 50 % probability level except those for the hydrogen atoms which are represented by spheres of a fixed arbitrary radius. The single lines represent the hydrogen bonds.

0.566 to 0.477 and a subsequent difference Fourier map gave the positions of the remaining five atoms in the terminal diethylamine group. After one cycle of isotropic and two further cycles of anisotropic refinements with all of the nonhydrogen atoms lowered the R value from 0.278 to 0.085, all of the hydrogen atoms were located in a difference Fourier map. In the final cycle of refinement the thermal parameters of the hydrogen atoms were not refined but were assigned as the isotropic equivalents of the atoms to which they were bonded. The function minimized in the refinement was $\Sigma\omega(|Fo|-k|Fc|)^2$ where k is a single scale factor and $\omega = 1.0$ for all of the reflections. The atomic scattering factors are from the International Tables.[6] The final R value was 0.055 for the 1524 observed reflections. The final atomic parameters are listed in Table 2*.

Results and Discussion

The stereoview of the molecule with the atomic numbering scheme is given in Figure 1. The bond distances and angles are listed in Table 3. The bond distances in metoclopramide are consistent within 2σ with those in its hydrochloride salt[2] except C(2)-O (1)and C(8)-N(2). The distances of 1.346 and 1.316 Å in the present study are 3σ and 4σ shorter than those in the salt respectively, but are not unusually short ones. The average C-N distance in the unprotonated triethylamine group is 1.454 Å in metoclopramide and 1.461 Å in procaine[8], a local anesthetic, which also contains the triethylamine group attatched to the p-aminobenzoate moiety. However, in the protonated triethylammonium group in the salts of metoclopramide[2] and procaine[9,10] the average C-N distance is 1.51 Å and thus exceeds the commonly observed C-N single distance of 1.47 Å, which may be associated with the increased coordination number of nitrogen on protonation.

*Tables (5 pages) for the observed and calculated structure factors and the bond angles involving the hydrogen atoms are available as supplementary materials from the author.

TABLE 3: Bond Lengths (Å) and Bond Angles(°) In Metoclopramide. Estimated Standard Deviation in Parentheses is for the Least Significant Figure

C(1)-C(2)	1.405(8)	C(2)-C(3)	1.395(9)
C(3)-C(4)	1.378(9)	C(4)-C(5)	1.386(8)
C(5)-C(6)	1.381(9)	C(1)-C(6)	1.375(8)
C(2)-O(1)	1.346(7)	O(1)-C(7)	1.426(7)
C(4)-N(1)	1.365(9)	C(5)-Cl	1.736(6)
C(1)-C(8)	1.508(8)	C(8)-O(2)	1.227(7)
C(8)-N(2)	1.316(7)	N(2)-C(9)	1.458(8)
C(9)-C(10)	1.514(9)	C(10)-N(3)	1.146(9)
N(3)-C(11)	1.443(9)	C(11)-C(12)	1.504(15)
N(3)-C(13)	1.459(8)	C(13)-C(14)	1.502(11)
N(1)-H(N11)	0.66(7)	N(1)-H(N12)	0.95(6)
C(3)-H(C3)	0.82(6)	C(6)-H(C6)	0.81(6)
N(2)-H(N2)	0.83(7)	C(7)-H(C71)	1.12(7)
C(7)-H(C72)	1.05(7)	C(7)-H(C73)	0.97(7)
C(9)-H(C91)	1.13(6)	C(9)-H(C92)	0.90(6)
C(10)-H(C101)	1.02(7)	C(10)-H(C102)	1.05(7)
C(11)-H(C111)	0.89(7)	C(11)-H(C112)	0.93(7)
C(12)-H(C121)	0.99(8)	C(12)-H(C122)	0.86(8)
C(12)-H(C123)	1.04(8)	C(13)-H(C131)	0.89(7)
C(13)-H(C132)	0.98(7)	C(14)-H(C141)	0.85(7)
C(14)-H(C142)	0.94(7)	C(14)-H(C143)	1.05(7)
C(1)-C(2)-C(3)	119.3(6)	C(2)-C(3)-C(4)	122.7(6)
C(3)-C(4)-C(5)	117.2(6)	C(4)-C(5)-C(6)	120.8(6)
C(5)-C(6)-C(1)	122.4(6)	C(6)-C(1)-C(2)	117.5(6)
C(8)-C(1)-C(2)	126.2(6)	C(8)-C(1)-C(6)	116.2(6)
O(1)-C(2)-C(1)	118.3(6)	O(1)-C(2)-C(3)	112.4(5)
C(2)-O(1)-C(7)	118.9(5)	N(1)-C(4)-C(3)	121.6(6)
N(1)-C(4)-C(5)	121.1(6)	Cl-C(5)-C(4)	119.6(5)
Cl-C(5)-C(6)	119.5(5)	C(1)-C(8)-N(2)	128.6(5)
C(1)-C(8)-O(2)	119.3(5)	O(2)-C(8)-N(2)	122.2(6)
C(8)-N(2)-C(9)	121.9(5)	N(2)-C(9)-C(10)	109.5(5)
C(9)-C(10)-N(3)	113.8(6)	C(10)-N(3)-C(11)	109.8(6)
C(10)-N(3)-C(13)	109.9(6)	C(11)-N(3)-C(13)	110.8(6)
N(3)-C(11)-C(12)	115.6(8)	N(3)-C(13)-C(14)	112.6(6)

The N(1) –C(4) bond of 1.365 Å is of typical distance when the benzene ring shows the small but significant contribution of the quinoid structure as found in *p*-aminobenzoic acid[11] and procaine[8]. However the single bond distance of 1.508 Å of C(1) - C(8) and the C-C bonds in the benzene ring indicate that there is no distinctive contribution of the quinoid structure in metoclopramide and no delocalization of the π electrons between the benzene and the amide group. Although the addition of chlorine and the methoxy group abolish the quinoid structure, the amino nitrogen still adopts an sp² hybridization and the π electron of the benzene ring are delocalized through the C-N bond. The dimensions in the amide group are similar to those in the peptide bond[12].

The benzene ring is essentially planar within experimental error as listed in Table 4. The substituents are also in the plane. It has been observed from the numerous crystal structures that the methoxy group in the benzene ring characteristically takes a planar conformation in spite of the absence of steric hindrance.[13] This preference has been rendered as a result of the favorable contribution to the crystal packing energy. In metoclopramide the methoxy group is also in the ring plane. The amide group is also planar and rotated only by 6.1° from the ring plane.

The amide nitrogen atom is strongly hydrogen bonded to the methoxy oxygen forming a six-membered planar ring. It is worthy to note that the valence angle C(2)-C(1)-C(8) of 126.2° deviates quite significantly from the ideal sp² geometry, presumably in order to accomodate the intramolecular hydrogen bond. This N(2) atom is also weakly hydrogen

TABLE 4: Equations of the Least-Squares Planes and Deviations of the Atoms from the Planes in Metoclopramide

(a) LS plane through the atoms of benzene ring

$0.8917x + 0.4058y - 0.2005z = 1.6322$

C(1)*	0.004 Å	Cl	0.004
C(2)*	0.004	C(8)	0.073
C(3)*	−0.014	C(7)	−0.144
C(4)*	0.016	O(2)	0.015
C(5)*	−0.008	N(2)	0.197
C(6)*	−0.002	C(9)	0.320
O(1)	−0.004	H(C3)	−0.134
N(1)	−0.022	H(C6)	0.085

(b) LS plane through the atoms in amide group

$0.9023x + 0.4204y - 0.0952z = 1.7451$

O(2)*	0.019	H(N2)*	0.029
C(8)*	−0.018	C(1)	−0.045
N(2)*	0.029	C(9)	0.045

*Atoms included in the calculation of the least squares planes.

bonded to the tertiary amine nitrogen N(3) in a bifurcated mode. Therefore it seems to be mainly the amide nitrogen atom that plays a major role to determine the overall conformation of the molecule.

The benzamide parts of the molecules in metoclopramide and its salt are conformationally very similar. The major difference is in the relative orientation of the benzamide and the triethylamine groups. This is represented by the difference in the torsion angle τ_2(C(8)-N(2)-C(9)-C(10)) as listed in Table 5. This difference apparently comes from the different intramolecular hydrogen bonding patterns in both molecules. In the salt N(3) is hydrogen bonded to the π electrons of
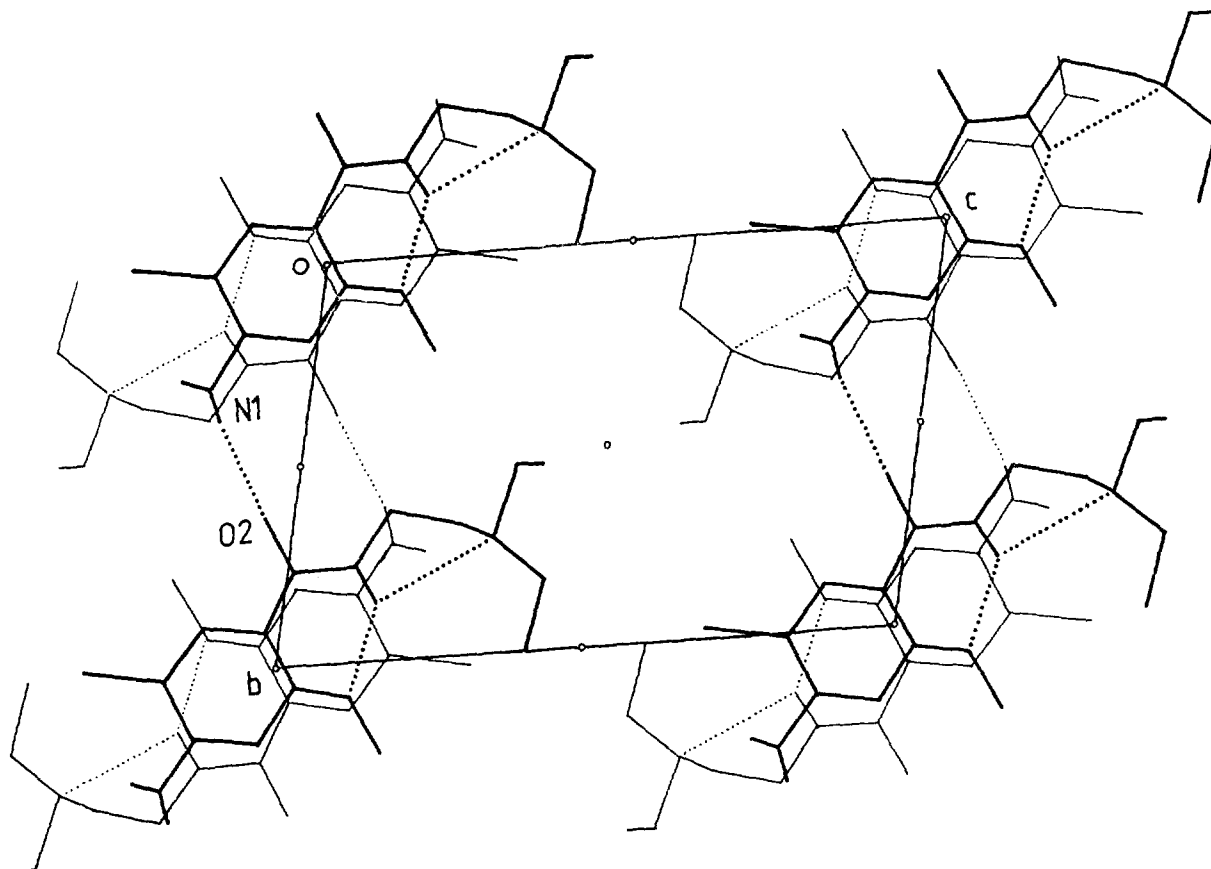

Figure 2. The molecular packing diagram viewed down the *a* axis of metoclopramide. The dotted lines represent the hydrogen bonds. Only the hydrogen atoms involved in the hydrogen bonds are drawn for clarity.

N(2) and thus acts as a hydrogen bond donor, while N(3) in metoclopramide is an acceptor.

The torsion angle τ_3(N(2)-C(9)-C(10)-N(3)) determines whether the aliphatic side chain is extended or bent relative to the benzamide moiety. It is $-71.1°$ for metoclopramide and $-62.7°$ for its salt respectively so that the whole molecule takes a bent conformation. This *gauche* conformation at C(9)-C(10) bond seems to be a characteristic feature in the structures containing the triethylamine group regardless of its protonation state. It is also *gauche* in nine procaine-related compounds.[8] The triethylamine group itself is conformationally labile and the conformation of each ethyl side chain seems to be determined by the crystal packing forces.[14]

TABLE 5: Torsion Angles in Metoclopramide Structures

		A	B
τ_1 :	C(1)-C(8)-N(2)-C(9)	$-177.7°$	$176.8°$
τ_2 :	C(8)-N(2)-C(9)-C(10)	-175.3	111.6
τ_3 :	N(2)-C(9)-C(10)-N(3)	-71.1	-62.7
τ_4 :	C(9)-C(10)-N(3)-C(11)	-81.0	-49.9
τ_5 :	C(9)-C(10)-N(3)-C(13)	156.9	-176.5
τ_6 :	C(10)-N(3)-C(11)-C(12)	170.6	-63.1
τ_7 :	C(10)-N(3)-C(13)-C(14)	-74.3	-65.6

A; unprotonated metoclopramide in this study
B; protonated metoclopramide in the hydrochloride salt[2]

TABLE 6: Selected Intermolecular and Intramolecular Contacts

Atom			Distance, Å		Angle,°	Position
a	b	c	a-c	b-c	a-b-c	of c
A. Intramolecular Hydrogen Bonds						
N(2)-H(N2)	...O(1)		2.672	2.09	127	x, y, z
N(2)-H(N2)	...N(3)		3.033	2.72	104	x, y, z
B. Intermolecular Hydrogen Bond						
N(1)-H(N11)	..O(2)		2.966	2.32	168	$x, -1+y, z$
C. Close Contacts (<3.6Å) in $\pi-\pi$ Interaction						
C(1)		C(3)	3.487			$-x, 1-y, -z$
C(1)		C(1)	3.558			$-x, -y, -z$
C(1)		C(2)	3.561			$-x, -y, -z$
C(2)		C(8)	3.346			$-x, -y, -z$
C(2)		C(4)	3.506			$-x, 1-y, -z$
C(3)		C(8)	3.573			$-x, -y, -z$

The molecules in the crystal lattice are linked by the N(1)-H$\cdots$O(2) hydrogen bonds forming the molecular ribbons along the *b* axis as shown in Figure 2. Along the *a* axis the centrosymmetrically related molecules are held together by the $\pi-\pi$ interaction between the part of the benzene ring and the amide carbon atom as represented by the short interatomic distances listed in Table 6. Along the *c* direction the only contacts between the molecules are hydrophobic interactions of the ethyl side chains.

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